MANUAL OF THE
PENICILLIA

A MANUAL
OF THE
PENICILLIA

BY

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PREFACE

Mycologically, *Penicillium* as the generic name of a group of green molds has been known for one hundred and forty years. Studies in this group were mainly floristic up to 1890. Green molds were everywhere and names for them appeared in every enumeration of the fungi of a particular locality, or of the species encountered in the study of decomposing or fermenting substances. Saccardo (1880) followed by Wehmer (1894, 1895) reported Penicillia active in the destruction of citrus fruit. Wehmer (1893) reported certain of them to be active producers of citric acid. Johan-Olsen (Sopp) (1898) related them to the cheese industry. The development of culture laboratories during this period made possible their isolation and examination in pure culture, and subsequent physiological studies led to increasing interest in their presence and significance.

Nevertheless, intensive study of the Penicillia was limited to less than a dozen laboratories including those of Wehmer, Bainier, Sopp, Thom, Westling, Biourge, Zaleski, Van Beyma, and Raistrick until the antibiotic penicillin was brought to America in 1941. Thenceforward, instead of individuals or small groups, hundreds of workers including bacteriologists, pharmacologists, chemists, and chemical engineers turned their attention to the Penicillia. Instead of a casual academic pursuit, the identification of these organisms became a matter of prime biochemical and industrial importance. A restudy of the genus seemed urgent.

Thom's Monograph, *The Penicillia*, was published in 1930. In the intervening years various new surveys have been made, many new species have been described, and biochemical investigations have directed special attention to many selected species. Finally, the development of penicillin shifted the emphasis from single strains, often discussed as species, to the recognition of groups of variants bridging many of the gaps separating strains formerly given varietal or specific rank. Meanwhile, the accumulation of large numbers of strains representing all of the major groups made available sufficient material to support a systematic restudy of all of the Penicillia.

Upon the establishment of the Northern Regional Research Laboratory of the Bureau of Agricultural and Industrial Chemistry, U. S. Department of Agriculture, at Peoria, Illinois, the development of a collection of pure cultures of micro-organisms significant to agriculture and industry was undertaken. Raper, who had worked with Thom for the preceding decade, was transferred from the Laboratory in Washington to take charge and brought with him cultures of all molds from the Thom Collection. Upon the retirement of Thom in 1942, all records and descriptive material ac-

cumulated by him at Storrs, Connecticut, and subsequently in the various laboratories in Washington which came under his direction, were transferred to Peoria. The Collection so established at the Northern Laboratory has been enormously increased during the past eight years by the isolation of new materials from many natural substrates, by the contribution of cultures by many collaborators, and finally through the cooperation of Dr. Johanna Westerdijk who in 1946 contributed transfers of all of the Penicillia in the Centraalbureau at Baarn.

The first obligation of a monographer of the Penicillia is to report as truly as possible what his predecessors described under particular names. His ideal is to produce as complete and as faithful a presentation as possible of the work of his predecessors supplemented by his own observations and knowledge. In contrast to the monographer, the writer of a manual of the Penicillia must begin with the establishment of a genus concept, then account for all species that have been assigned to it. He may correct, redescribe, reassign, or reduce to synonymy any specific name and description encountered, *so long as his own descriptions lead to the identification of actual material,* and to the assignment to that material of Latin names which are correct according to accepted rules of nomenclature. His primary obligation is to the investigator who needs to identify an organism. The manual must in addition furnish such guides to the literature as will permit the critical worker to search original sources for himself whenever he requires more detailed information than the manual supplies.

With this background and philosophy the preparation of this Manual was undertaken. The monographic feature of Thom's earlier work (1930) has been dropped. The concept of series, i.e., groups of strains having fairly consistent morphology and usually showing related biochemical activities, is emphasized. Within each series recognized species are arranged in what we consider to be a logical sequence, and the reasons for their recognition are indicated. The punctilious systematist will find that the description of a species of *Penicillium* is no longer a "photograph-like" presentation of the first strain or type as found, but represents instead a composite of characters selected as the result of continued cultivation of many strains. Such a concept is sufficiently broad and elastic to include the usual range of variants which the experienced worker will naturally expect. At the same time we have attempted to establish species limits with sufficient clarity to exclude forms which are unrelated and forms which may present only superficial evidence of relationship.

This Manual is designed primarily as a means for identifying Penicillia which may be encountered in the laboratory or which for some reason may be significant in microbiological or biochemical processes. It is

hoped that it will minimize misunderstandings in the interpretation of species as described and understood by our predecessors. In addition it is intended as a guide by which the investigator may reach the accumulated literature relative to the activities and significance of these molds.

Although the plans for this book had long been tentatively formed and the materials partially segregated into fascicles, actual preparation followed the suggestion of Dr. W. J. Robbins, then Chairman of the National Science Fund, that help to speed up the completion of the book might be found. In the Spring of 1945 the George F. Baker Charitable Trust Fund made available to the National Science Fund a sum sufficient to provide the services of professional, technical, and clerical personnel necessary to carry out the work. Thereupon a cooperative agreement was drawn up between the Department of Agriculture and the National Science Fund and work on the project was initiated in June 1945. The cooperation of the Northern Regional Research Laboratory in providing the time of the senior author, in supplying space and equipment, and in performing multitudinous administrative details has been essential to the completion of the task.

Since fully two thousand strains in addition to our own original Collection of at least as many more have been studied, it is impractical to recognize here the contributions of the many workers who cooperated by furnishing cultures. Acknowledgments are made in the text wherever their organisms are discussed.

In the preparation of this manuscript and in the cultural studies upon which it is largely based, important contributions have been by May H. Flickinger and Jane A. Roberson who made cultures for examination and prepared lyophilized preparations of the strains discussed in the text; by Roland W. Haines and Robert F. Garrett, photographers at the Northern Regional Research Laboratory, who made all of the color pictures as well as the black and white photographs of plate cultures; and by Kathryn E. Dore who typed the manuscript in its final form.

The authors are indebted to the Chas. Pfizer & Co., Inc., Brooklyn, New York, for underwriting the cost of reproducing the natural color photographs.

Administratively, many individuals have contributed to the cooperative project under which this manuscript was prepared. These include W. J. Robbins and Harlow Shapley, Chairmen of the National Science Fund; O. E. May and F. B. Howard, Chiefs of the Bureau of Agricultural Chemistry and Engineering; and H. T. Herrick and G. E. Hilbert, Directors of the Northern Regional Research Laboratory.

THE AUTHORS

PART I

GENERAL DISCUSSION

Chapter I

HISTORICAL

Species of *Penicillium* are so abundant and so conspicuous in all sorts of stale or decaying organic matter that they constitute a part of the common conception of mold and are loosely referred to as 'blue' or 'green' mold. It is easy to guess, therefore, with Brefeld that some *Penicillium* furnished the material for *Aspergillus albus* in figure 3, table 91, of Micheli's "Nova Plantarum Genera" in 1729. Again, it is common mycological tradition that *Mucor crustaceus* of Linnaeus represented some *Penicillium*. This name passed from author to author thereafter without added information from real study of specimens. Persoon (1797–1801) appears to have included the species in his conglomerate genus *Monilia*, again with very little evidence of study under higher magnifications. Some think that Linnaeus' species reappears in *Penicillium crustaceum* Fries (1829), but there is no continuity in materials and no evidence of real study. Saccardo *in the Sylloge in 1886 (Vol. IV, p. 78) went so far as to cite Monilia digitata* Persoon as the basis of *P. digitatum*, although he furnished little proof of the continuity of this view even as tradition. Bulliard (1809) used the name *Mucor penicillatus* for these "broom" or brush-like forms and provided the first reasonably adequate illustration of a mold unquestionably representing a *Penicillium* (fig. 1).

The name *Penicillium* applied to a genus of fungi first appears in Link's "Observationes" (1809), in which he described very briefly the genus and three species: *Penicillium glaucum*, *P. candidum*, and *P. expansum*. Close scrutiny of these descriptions and all accessory information gives no clue to the identity of the molds which Link actually had under his microscope as *P. glaucum* and *P. candidum*, except that they presented the general appearance of the familiar penicillus or brush seen in the microscopic examination of Penicillia. *Penicillium expansum* was designated as the fruit rot which in Berlin at that season clearly pointed to the *Penicillium* rot of apples and related fruits (see Thom, 1930). We can, therefore, be reasonably certain of *P. expansum* Link as a recognizable generic type, world wide in distribution. It is regrettable that Link in 1824 abandoned his species *P. expansum* and called all the green Penicillia *P. glaucum*. This practice has been followed by many workers to the present day with the result that use of the name *P. glaucum* now gives little clue to the real identity of a *Penicillium*.

Link's contemporaries, such as Persoon, Fries, and Greville (1823 to 1828), accepted Link's genus *Penicillium*, although their publications

and Broome (1881 1882) Spegazzini (1895–1896) Cooke (1871 to 1891), and even Saccardo all of whom were active, primarily as collectors and brought to light many species of real value among groups which make more satisfactory herbarium specimens The assumption that whatever was found in nature undisturbed by man was normal early became dominant and still persists in much of the taxonomic literature

Many years were required for mycologists to realize that among these molds much of what we now loosely call morphology represents response to environment For example a mold grown in the presence of a fermentable sugar may show one aspect, whereas the same mold if grown on a leather shoe or some other nitrogen rich substrate may assume a very different appearance If grown in mixtures with other molds and bacteria the colonies of a particular culture often lose identifying characters based upon its development in some other environment Thus the idea of growing molds in pure culture under standardized conditions as a basis for taxonomy gradually developed

DeBary s laboratory began to report work with cultures of molds between 1850 and 1860 It was not however until Brefeld published the life history of *Penicillium glaucum* in 1874 that real cultural study of the Penicillia was initiated He limited the discussion to one species *P glaucum* which is nowhere in his paper fully described although structures encountered at each stage of its life history were described in detail and elaborately figured Part of these figures show evidence of being drawn from actual preparations others are obviously schematic and present Brefeld s interpretation of his observations The method of conidium formation was evidently not understood but the general structure of the penicillus was beautifully developed The formation of perithecia as hard sclerotium like masses of pseudoparenchyma followed by the slow development of ascogenous central areas was described and illustrated although such were not to be unmistakably reported again until the studies of Dodge (1933) van Beyma (1929 1933) and Shear (1934) more than fifty years later Brefeld states that he was working with the common *P glaucum* which is generally interpreted as approximating *P expansum* Link as we know this species today His work was done with the cruder methods of culture which preceded the rise of bacteriology with its provision for protecting cultures against contamination hence it is not surprising if the various drawings presented suggest the probability that more than one species was involved in his series of cultures One of his figures depicting a coremium from a rotting pear apparently represents some strain of *P expansum* and the figures of some of his penicilli closely approximate this species except that conidia are generally elliptical (fig 7B) rather than globose as shown in Brefeld s figures (fig 2) The peri

give little evidence that any one of them actually knew which organism another had described under any of the different names proposed

In *Penicillium*, as in *Aspergillus*, Corda (1837 to 1839) cleared up some of the uncertainties of structure evident in previous discussions of the genus, but his illustrations idealized the morphology of his species to such an extent that subsequent identification has never been satisfactory Species of *Penicillium* are found described in the works of Bonorden Fresenius, and Preuss during the period about 1850 These authors included with what we now call *Penicillium* such organisms as *Cladosporium*, *Hormodendrum* or even *Monilia sitophila* Few, if any, of the names they proposed can now be recognized as Penicillia The e workers represent a



FIG 1 Bulliard s Plate 504 fig XI *Mucor penicillatus* The earliest known figure unmistakably representing a *Penicillium*

period in which the mycologist was primarily a microscopist intent upon describing the specimens which came to hand either as fresh materials from his own environment or as herbarium specimens A corollary to his work was the assumption that a mold found in any situation was sufficiently pure and characteristic to form a safe basis for taxonomic work No cultures were made The reactions of one organism to the presence of one or several others were not taken into account The specimen was described then labeled and dried for the herbarium and the description was published whether or not the specimen was recognizable after it was so preserved Montagne (1856) lamented that no one could find out what organism any of his predecessors used in describing their species but he failed to offer a more efficient handling

The same difficulty is encountered in interpreting the species of *Penicillium* described by Rivolta (1873) Berkeley (1841 1875), Berkeley

thecia as described and illustrated both in form and development, approximate those seen in strains now assigned to species in the *Carpenteles* and *P. javanicum* series (fig. 2). Other of his penicilli might belong to some species such as *P. egyptiacum* van Beyma or possibly *P. asperum* (Shear) in which case they might easily have developed upon the same mold that produced the sclerotioid perithecia with tardy ascospore formation. His ascospores with equatorial ridges and rough side walls could have belonged to some species such as *P. asperum* or *P. baarnense* van Beyma. No one can be certain whether Brefeld worked with a mixture of two species, or whether he worked with a single *Penicillium* and some of his drawings (obviously schematic) are misleading, or whether he worked with a single strain and illustrated it accurately throughout. We can say, however, that no single species is known to us which combines all of the characteristics illustrated by Brefeld. When one considers the level of laboratory culture techniques of his day and the state of mycological knowledge then existing, one cannot but admire the skill and care exhibited in his work.

The use of the name *Penicillium glaucum* for the apple rot organism was continued in Sopp's Monograph (1912, p. 48) and in Wehmer's Beiträge (1893). Both men were students in Brefeld's laboratory, hence the continuity of the usage is evidence of an understanding among them that this organism should be regarded as *P. glaucum*.

Wehmer in 1895 published his studies of the Penicillia occurring upon rotting fruit. He figured and described the destructive effects of *Penicillium expansum* on apples, pears, and grapes—but under the name *P. glaucum*. The olive colored rot of oranges already described by Saccardo as *P. digitatum* in 1880 and distributed in Mycotheca Italica was called *P. olivaceum* and the soft rot organism with blue green colors was correctly regarded as new and named *P. italicum*. In the same year he published his study of citric acid forming molds, to which he gave the name *Citromyces*, and his study of ascospore formation in *P. luteum* Zukal. Wehmer was the first investigator to pay particular attention to the physiological and biochemical activities of molds, and he prepared the studies of this group in the second edition of Lafar's Technische Mykologie (1906).

Sopp[1] records that he recognized as early as 1890 that the name *Penicillium glaucum*, in addition to designating the apple rot organism, was being used to cover more than a single species. Elfving came to the same conclusion in 1895. In 1898 Sopp separated certain of the forms found active in cheese ripening as *P. aromaticum*. Unfortunately his descriptions of these organisms were entirely inadequate, apparently depending for identification primarily upon their presence upon particular varieties

[1] Early papers signed Olav Johan-Olsen

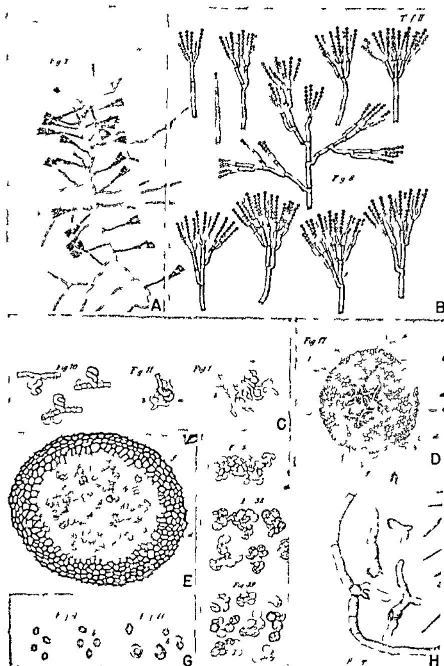


Fig 2 Brefeld's figures of *Penicillium glaucum* reassembled (in part) *A* Habit sketch showing origin of conidial structures × 75 *B* Detailed drawings of penicilli × 400 *C* Initial stages in perithecium formation × 400 *D* Young perithecium with fertile ascogenous hyphae beginning to appear × 175 *E* Mature perithecium containing asci and ripe ascospores at center × 175 *F* Developing asci showing their characteristic origin in chains × 400 *G* Mature and germinating ascospores × 500 *H* Germinated ascospores × 500 (After Brefeld 1874.)

1897 After Dierckx published his "Essai" Biourge took up the task in earnest He gave a brief survey of this work in a conference at Louvain in 1916 which was published as a pamphlet in 1920 followed by his Monograph in 1923 In this latter work Biourge followed along the culture lines already proposed by Dierckx broadened his work to cover most of the studies made by Thom and gave a brief Latin diagnosis for some 125 species followed by culture notes in French The descriptions were supplemented by line drawings of the conidiophore penicillus and conidia and colored plates showing the colors and color changes of his colonies It represented beyond question the most comprehensive and elaborate study of the genus made up to that time

Unfortunately Biourge's microscopic work was largely done from fruiting structures removed from cultures preserved in alcohol Furthermore he paid little attention to the colony habit with its large contribution to our knowledge of the organism as it grows in the culture tube or petri dish In the main Biourge had a fairly good idea of the group relationships within the genus *Penicillium* and certain of his divisions are tangible enough entities His Radiata covering what we now recognize as the *Penicillium chrysogenum* series is illustrative

Biourge's conception of the genus in the broadest sense called for the inclusion not only of *Coremium Citromyces* and of more or less related series like *Scopulariopsis Gliocladium* and *Paecilomyces* but part or all of several other genera in which figures or descriptions offer suggestions of a penicillate conidial apparatus

Zaleski (1927) described as new thirty five species and one variety of *Penicillium* from the forest soils of Poland His descriptions go into unnecessary detail regarding the buckling and wrinkling of colonies upon gelatin as the substratum becomes liquefied Methods of microscopic observation followed Biourge to the destruction of much useful information regarding the structure and appearance of the conidium producing organs as they are developed in the colony His cultures and notes were sent to Biourge whose comments are given for certain species but whose opinions were not always followed In the main however he accepted the subgenus section subsection and series divisions as given in Biourge's Monograph and fitted his species into this scheme insofar as possible He apparently confined his study to the soil organisms which he isolated hence had no background of comparative knowledge of the many cosmopolitan saprophytes already recognized as belonging to the genus Careful comparative study has tended to reduce most of his species to synonymy with other species previously described

Thom in his comprehensive Monograph brought together all of the material on the taxonomy of *Penicillium* published up to that time (1930)

of cheese Even in his Monograph (1912) this usage remains too indefinite to be verified His Monograph brought together a mass of descriptive matter and many figures covering some sixty species of *Penicillium*, together with descriptions and illustrations (some colored) of forms which he thought to be closely related Despite the mass of data presented, very few of his species have been identified with certainty by other workers Insofar as we know, he never distributed any cultures

Dierckx published his "Essai" in 1901, in which he sketched his method of work and proposed a series of twenty five new species with descriptions so brief and inadequate that no one working with the published material succeeded in identifying any of his new species As noted by Saccardo in the Sylloge, the new names proposed were not supported by descriptions or figures which would identify them He appears however, to have left in the laboratory at Louvain, colored plates descriptive material, and sufficient of his cultures to enable Biourge to reidentify and redescribe twenty two of these forms in 1923 Biourge obviously based his recognition and perpetuation of some of Dierckx s specific names upon the accessory material left by Dierckx

Thom began to study Penicillia in connection with cheese investigations in 1904 published "Fungi in Cheese Ripening in 1906, his Cultural Studies of species of *Penicillium* in 1910, and his group concept of classification of the Penicillia in 1915 In these papers the necessity of comparative culture upon standardized media was stressed in contrast to the search for optimum conditions of culture organism by organism

Weidemann in Kiel (1907) and Westling in Stockholm (1911) used careful cultural methods in describing their series of green Penicillia But neither worker had a large enough collection nor followed the study long enough to determine group relationships

Bainier, under the general title Mycotheque de l'Ecole de Pharmacie" (Paris) began publishing descriptions of species of *Penicillium* in 1905 and continued partly separately partly with Sartory, until 1914 In this series of species many forms were described and figured with meticulous care, hence some of them are readily identified Efforts were made to maintain all of these forms in culture at l Ecole de Pharmacie Bainier separated the form described later by Thom (1910) as *Penicillium divaricatum* and made it the type of his genus *Paecilomyces* (1907) He also designated *P brevicaule* Saccardo, with its numerous allied forms as the basis of a new genus *Scopulariopsis* (1907) The separation of both of these groups from *Penicillium* can be readily justified upon the ground of lack of essential relationship Bainier adopted Wehmer s genus *Citromyces* and described his monoverticillate strains as species under that name

Biourge, under the stimulus of Carnoy, began to study Penicillia in

little more than guesses Such species and varieties will be found only in the Species Index (Chapter XVIII)

Following Brefeld's work Zukal in 1889 described *Penicillium luteum* as an ascosporic form with the unmistakable conidial apparatus of a biverticillately symmetrical *Penicillium* Asci were borne throughout a loose network of hyphae almost if not completely lacking a perithecial wall From that description Saccardo without examining material (Sylloge 11 137 1895) transferred the species to *Gymnoascus* as *G luteus* (Zukal) Saccardo Zukal described elliptical ascospores ornamented with a spiral band passing 2 to 3 times around the cells Wehmer (1893) clearly illustrated the same type of spore For many years thereafter no one found such an organism in culture although many related organisms were collected Derx (1925–1926) reported having had one Professor Bisby sent one to us from Manitoba in 1933 which was included in Emmons study of the ascocarps in *Penicillium* (1935) One or two others have been seen Subsequent to Zukal's description of *P luteum* other workers including Klocker (1903) Dangeard (1907) Thom and Turesson (1915) Lehman (1920) Emmons (1935) Swift (1932) and Raper and Fennell (1948) reported a number of ascosporic Penicillia showing the general series characteristics of Zukal's species but differing in specific details

Examination of organisms identified as species of *Gymnoascus* reveals ascogenous structures closely related to the *Penicillium luteum* series Detailed search through colonies of certain species of *Gymnoascus* discloses very simple penicilli consisting of short conidiophores and groups of one two or rarely more sterigmata bearing chains of conidia One is compelled to believe that *Penicillium* and *Gymnoascus* come very close to each other morphologically in the *P luteum* series

In another series typified by *Penicillium javanicum* van Beyma (1929) the perithecium first develops as a pseudoparenchymatous mass of polyhedral thick walled cells at the center of which an ascogenous core subsequently arises and by enlargement gradually comes to occupy the entire body except for a firm wall or peridium few to several cells in thickness Other monoverticillate species with perithecia of this same general character have been described by Klebahn (1930) Dodge (1933) and Raper and Fennell (1948) The same process of perithecial development occurs in the *Carpenteles* series noted above but the penicilli in these latter forms are typically biverticillate and asymmetrical and the forms are placed in the Divaricata

Langeron (1922) on purely bibliographic grounds created the genus *Carpenteles* for Brefeld's *Penicillium glaucum* but since he studied no cultural material the genus went unaccepted until Shear (1934) attached it

Chapter 1

EMBRYOLOGY OF THE UPPER ALIMENTARY TRACT

CHARLES F DE CARIS

Prior to the third week the embryo is a flattened disk on the umbilical vesicle (yolk sac) It constricts from the vesicle by confluent cranial lateral and caudal sulci Cranial parts include the tubular foregut middle parts the midgut opening to the vesicle (until the sixth week) caudal parts the tubular hindgut This chapter deals with the embryology of the foregut and midgut parts specifically the esophagus stomach and small intestine These parts are fairly uniform in development with regional differences in details of size shape glandular specialization and positional changes The inner tube of entoderm is the primary tissue forming the epithelial lining of the digestive tract and the glandular elements This inner tube is invested with splanchnic mesoderm as connective tissue muscle and mesothelium Cranial levels of the tube specialize earlier than caudal levels ("principle of developmental direction") and the epithelium growing more rapidly than the outer wall is thrown into folds which greatly increase its surface area Of the two main muscle coats the circular develops at six to seven weeks the longitudinal at twelve weeks The muscularis mucosae appears at twelve to twenty four weeks

THE ESOPHAGUS

Embryos of about 2 5 mm lack a definite esophagus as in fishes and at four weeks the esophagus is but a short tube from pharynx to stomach The trachea is separated from the tracheogular primordium at 4 mm by two bilateral laryngotracheal grooves closing off the esophagus dorsally Thereafter the esophagus elongates rapidly pacing the differentiating neck and the fast growing heart and lungs At six weeks its epithelium is in two layers a week later it has proliferated and become vacuolated forming irregular channels But at no time is the human esophagus a solid cord as in birds and reptiles[2,3] At birth the lining is ten layers of stratified squa mous epithelium with some ciliated cells Superficial glands develop at four months deep glands external to the muscularis mucosae appear much later

Errors of development result in stenosis (stricture) or atresia (lack of lumen) The most serious anomalies are fistulas from the trachea to the lower esophagus the upper esophagus in such cases usually being atretic these fistulas result from incomplete separation of the laryngotracheal groove from the esophagus A membrane may occlude the esophagus when thin this membrane has been ruptured by the esophagoscope with result ing functional lumen[1]

THE STOMACH

In 4 to 5 mm embryos the stomach is a spindled enlargement of the foregut lying at a high level By the seventh weekend it has descended ten

However such a Mistake was particularly excusable in the Doctor, whose Erudition in *Medicine* and knowledge of Natural Philosophy was according to the unhappy State of Learning in his Country too weak to counter balance the deep and overbearing Impressions which *a great Number of new and extraordinary Facts* had made on his Imagination (Author s italics)

Others were less critical and more enthusiastic about Solano s great discoveries For example Fouquét while querying some finer details of Solano s views as to the kind of morbid material which produced the several kinds of irregular pulse defended Solano in no uncertain terms against Nihell s suggestion that lack of erudition might have vitiated his

Fig 2—Solano de Luque *Lapis Lydos Appollinis* Madrid 1731 Pp 96 and 97

work mais pourtant tout cela vaut son prix mais les decouvertes de Solano dureront au dela des siécles & les penibles chef d oeuvres des *erudits* semblables à des phosphores legers n auront fait qu éblouir un moment (*Essai sur le Pouls* 1767 p xxvij)

Solano s interpretation was accepted by Laennec (1819 § 675 p 236) La derniere espece d intermittence ou celle qui consiste dans l absence d une pulsation complete qui revient quelquefois avec une periodicite exacte à des intervalles plus ou moins eloignes le pouls etant d ailleurs regulier constitue le signe avant coureur de la diarrhée critique decouvert par Solano de Lucque Laennec also accepted Solano s teaching regarding the other varieties of irregular pulse

Doubts about the universally bad prognostic significance of the intermittent pulse based on grounds more similar to those of Willis and Lancisi were expressed by other

writers of the eighteenth century Amongst those may be mentioned E A Nicolai (1722–1802) According to his *Theoretische und practische Betrachtung des Pulsschlages* (1746) a distinction should be made between a pulse intermitting von Natur oder wegen einer ublen Beschaffenheit des Körpers and da ubrigens der Mensch gesund ist (we would say constitutionally in an otherwise healthy individual) and that variety due to widernatur liche Ursachen by which he understands conditions of the cardiovascular system such as polyps ulcera in the vessels ventricles or auricles (Ohrlaplein)

A similarly more discriminating assessment of the significance of pulse intermissions is found in Senac s (1693–1770) *Traite de la structure du coeur de son action et de ses maladies* (1749) He enumerates some of the different conditions which may give rise to such inter mittency and concludes that because of the varieties of causes the irregularity does not always denote the same condition In old people the inconstant pulse was due to the harden ing of the arteries due to dryness which cause an unsteady flow of the blood and the spirits in the nervous tubes The arrhythmias had a greater importance in malignant fevers He sums up by saying (p 217–8) En general de quelque espece que soient les intermissions elles ne suffisent pas seules pour qu on puisse prononcer sur la mort ou sur la vie si elles sont dangereuses comme on ne sçauroit en douter elles se sont souvent terminees heureusement c est ce qu on peut assurer sur le temoignage constant de l experience presque tous les Praticiens avouent qu apres des intermissions qui ne paroissoient laisser aucune esperance divers malades sont parfaitement gueris

Senac exemplified the intermittent pulse by the failure of a pulse to occur at the third second assuming an otherwise regular sequence of one pulse per second From this he distinguished the pouls intercadent celui ci consiste en ce qu il survient entre deux battements une pulsation qu on n attendait pas —which in retrospect may have been the first clear description of an interpolated extrasystole

Marquet (1747) described the various types of pulse in terms of a special musical nota tion The normal pulse was expressed as a crotchet between two horizontal lines normal rate was indicated by such crotchets being put at the beginning of a bar which was divided into five parts by equally spaced vertical lines A minim indicated a large pulse a quaver a small pulse and a semi quaver the vermicular pulse The position of the note denoted what we could now call the tension below the lower horizontal line a pouls concentre on the lower line a pulse more difficult to palpate than normal between the two horizontal lines normal tension and on or above the upper line types of pulse more easily palpated (pouls eleve and pouls superficiel) The different clinical conditions which were thought to give rise to the diverse types of pulse were described largely in Galenical terms

Regarding the significance of the intermittent pulse Marquet stated that generally it carried a bad prognosis But amongst the different varieties the pouls eclipse ou inter cadent and the pouls inegal were considered nearest the normal Regarding the for mer il bat regulierement pendant dix vingt & quelquefois trente pulsations plus ou moins puis il se concentre sans se faire sentir au tact ensuite il frappe fortement & brusque ment dela il continue son train a l ordinaire Marquet encountered this kind of pulse in subjects who were troubled only by frequent vapours and he believed it to be due to air bubbles circulating with the blood when these passed through the heart this could dilate only feebly and as a result cardiac systole and arterial diastole were imperceptible quasi suppressed His observation that this kind of pulse was liable to occur in divers was ex plained by the fact that they held their breath for a long time and that air compressed in the lungs entered the blood vessels In his musical notation the intermission is indicated by a space without a note the larger pulse after the intermission by a minim on the upper line in order to signify a larger and less easily suppressed pulse The stronger pulse after the intermission is attributed to the strong and brusque pulsation of the heart due to the greater quantity of blood in the heart after the intermission This description seems to be most

suggestive of abortive extrasystoles followed by a large post extrasystolic beat though dropped beats cannot be excluded (*See* Fig 3a)

The pouls inegal & intermittent also considered to approximate the normal pulse was characterized by occasional premature (un peu précipitees) pulsations (*see* Fig 3b)

The pouls inegal & intercurrent being without any regularity seems to correspond most closely to the pulse in auricular fibrillation

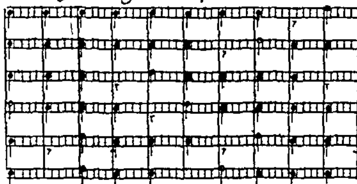


Fig 3a
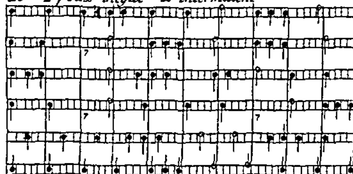


Fig 3b

Fig 3 —Marquet *Nouvelle méthode facile et curieuse pour connoitre le pouls par les notes de la musique* 2nd ed Amsterdam 1769 Figs 19 and 20

(For a reproduction of Marquet s musical notation of the *pouls caprisant vide* Bedford)

Marquet though well known for his method to express the various types of pulse in musical notation was not the first to do so More than a century before Hafenreffer (1587–1660) construed in 1641 a curious system of musical notation based on the Monochord (*see* Fig 4) The four lines indicate the four palpating fingers and some relationship was thought to exist between the Melodiae Cardinales & Radicales namely bass treble tenor and contralto and the four elements fire, air water and earth

Heberden (1710–1801) (paper read on 7th July 1768 published in 1786) denied that the intermitting pulse had any significance Some books speak of intermitting pulses as dangerous signs but I think without reason for such trivial causes will occasion them that they are not worth regarding in any illness unless joined with other signs of more moment He also observed that such arrhythmias may temporarily disappear in patients

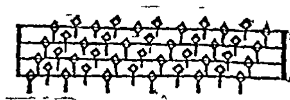
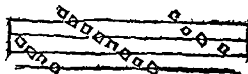


FIG 4a



Intempeſtive tempus perturbans modo bis feriendo, *Dicrotus* modò a ſaltu ſeu quodam hiatu capræ Italis Gazellæ dictæ, ſimilitudine ſumpta, nuncupatus habetur pulſus *Caprizans* Sicut enim dictum animal uno & eodem tempore duos ſaltus efficit, ultimum tamen celeriorem priore, 6 talem & arteria quandoque ſolet figurare.

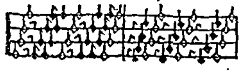


FIG 4b

FIG 4 —From Hafenreffer *Monochordon Symbolico biomanticum* 1641 *a* Pulsus moderatus (normal pulse) p 55 *b* Pulsus intermittens dicrotus and caprizans p 64

during illness and it was a never failing sign of their recovery when their arteries began again to beat in their unusual irregular manner

Morgagni (1682–1771) devoted much space to an extensive discussion of the intermittent pulse (1769) as the greater part of physicians are very greatly terrified thereby often with good reason yet frequently without any as when there is some cause of it in the stomach or intestines which may either vanish away of itself or be easily remov d by the

physician Amongst such causes he mentions flatus This may be an early description of what we may now regard as extrasystoles precipitated by way of reflex from the gastro intestinal tract

An instructive example of intermittency of the pulse most probably due to anxiety and certainly perpetuated by it as well as cured by appropriate treatment is contained in the following passage it concerns a certain very experienc d and judicious professor of physic at Bologna who worried greatly about his intermittent pulse yet the very same gentleman after having not disdain d to take my advice though a young man which was to apply his fingers to his pulse much less frequently and having in consequence thereof less increas d the anxiety of his mind upon the occasion the intermission soon became much less observable till at length by not attending to it it entirely vanish d away Morgagni had also observed that such intermittency may be due to cardiac factors or causes in the neighbouring trunk or both and then indeed I must confess it becomes a symptom of importance and we are under a necessity of considering it as such In such general form this view is acceptable to day for extrasystoles are known to indicate involvement of the heart in infectious diseases as well as sometimes being the first sign of an otherwise asymptomatic coronary sclerosis Discussing cardiac abnormalities in instances of inter mittent pulse Morgagni refuted the then common view that this arrhythmia signified the presence of polyps and also discussed critically the relations between intermittency of the pulse and valvular stenosis and dilatation of the heart In his own words What then are we to conclude? Will these causes which when separate from each other are always unable to produce an intermission of the pulse be always or almost always able to produce this symptom when they are join d together? As in order to discuss these points properly a much greater number of observations are requir d it will be sufficient at present to have pointed out those things which do not always answer What an impressive example of acute observations close reasoning and reserve in drawing conclusions Morgagni s approach is! Amongst the many valuable points contained in his writings there is also an early recog nition of the complexity of factors which may give rise to such arrhythmias an aspect which will become apparent as one of the central themes in the course of this book

Views similar to those of Senac and Heberden were held by Maximilan Stoll (1742–1787) According to him the significance of the intermittent pulse occurring during fevers varies according to the underlying condition He also observed that the arrhythmia in old people temporarily disappears during febrile illnesses and that the recurrence of the inter mittent pulse heralds recovery His writings were considered sufficiently important to be quoted by Nothnagel nearly a century later (1876)

Skoda (1805–1881) emphasized (1850) that while disturbances of cardiac rhythm may unquestionably be due to organic cardiac disease it was certain that the most pronounced irregularities can be encountered in otherwise normal hearts and that there was hardly any structural abnormality of the heart valvular or otherwise in which the heart action could not be entirely regular Aus der Unregelmassigkeit der Herzbewegungen wie gross sie auch seyn mag kann man deshalb nie den Schluss ziehen dass eine organische Krankheit des Herzens vorhanden sey (p 233)

However in spite of such writings Galen s view held sway until the beginning of the present century Fothergill (1872) stressed that cardiac intermittency was the most serious rhythmical disturbance of the heart and is a symptom ordinarily of very great import According to Lasegue (1872) it was associated with cachexia chronic or acute but since it was not indicative of une alteration substantielle de l organe it was of no prognostic significance However as it occurred only in general marked impairment of health it was considered an important clinical sign (The self assured manner of this paper particularly in its opening pages seems to contrast sadly with its above—not particularly constructive—contradictory conclusions)

Fothergill s tabular presentation of arrhythmias contained in his earlier paper of 1870 (*see* Table 1) is a good illustration of the ideas prevailing about cardiac arrhythmias at that time The complexity of conditions which may give rise to cardiac irregularities, became increasingly realized and interest shifted to the study of the underlying causes investigated by experiment and clinical observation

Cardiac Irregularity is due to Disturbance of Balances in—	1 Vis Inertiae of Blood = Muscular power	Increase in the vis inertiae by { Arterial obstruction / Altered chemical characters } Loss of muscular power { Loss of integrity from degeneration { Acute in fevers / Chronic as from atheroma } Exudation to substance (*Jenner*) / Altered nutrition from altered blood }
	2 Distension = Irritability of cardiac ganglia + controlling action of vagus	Excessive distension from temporary action of causes above Imperfect distension—as in severe haemorrhage—from want of blood to distend the chamber walls Exhaustion of sympathetic—from fatigue debauch withdrawal of nerve force for purposes of digestion &c Chronic cerebral disease &c—(*Richardson*)
	3 Cardiac Ganglia = Controlling action of the vagus	Constitutional peculiarity Transient mental conditions—(*Richardson*) Tumour of vagus—(*Romberg*) Action of cardiac neurotics { Exciting the cardiac ganglia—as digitalis belladonna &c / Paralysing the cardiac ganglia or exciting vagus— } as aconite Calabar bean &c

TABLE 1—From Fothergill J M (1870) Cardiac irregularity *Lancet* 2 851

Of the various factors tabulated by Fothergill as responsible for cardiac arrhythmias two seem to have attracted most attention the role played by the cardiac nerves and disproportion between the strength of the heart and the amount of work it had to perform with the additional importance of cardiac distension

Traube (1818–1876) was one of the protagonists of the importance of the cardiac nerves He was the first to specify the *pulsus bigeminus* as a clinical entity (substituting this term for his earlier one of zweispitzige Wellen = bifid waves) (1867 1872) and attributed this arrhythmia to a paralysis of the spinal inhibitory cardiac centres associated with increased irritability of the cardiac component of the inhibitory spinal nerves While Traube has to be given the credit for clearly distinguishing between the dicrotic pulse and *pulsus bigeminus* by starting a confusion between the latter and *pulsus alternans* he was to obscure the significance of these two conditions for a considerable time to come Both the bad prognosis which Traube attributed to the *pulsus bigeminus* and his explanation of this phenomenon were soon challenged (Rosenstein 1877) but the confusion between *bigeminus* and *alternans* persisted much longer (for instance Gerhardt 1896 Mackenzie 1902 p 94) (*see* also chapter on Coupling) Amongst those who considered the action of nerves as important in the origin of cardiac arrhythmias may be mentioned Nothnagel (1876) who emphasized abnormal activity of the automatic cardiac ganglia and the possibility of vagal stimulation by way of reflex and Baumgarten (1888) who mentioned as causes *inter alia* abnormal conditions in the medullary cardiac centre and disturbances of the cardiac nervous system both in its cerebral and intracardiac portions also reflexes originating from distant organs In a way Tripier s assertion of the constant association of a slow and arrhythmic pulse with epilepsy belongs to this conception

The view that disproportion between the strength of the heart muscle and the amount of work which it has to perform was the main cause of cardiac arrhythmias seems to have played an even greater role This was based on the observation that in certain circumstances increase in the resistance to cardiac outflow produced arrhythmias and led to the belief that such arrhythmias in man signified the presence of heart disease which impaired the heart s contractile power

Knoll and Heidenhain both in 1872 found experimentally that in certain circumstances raising the blood pressure resulted in cardiac irregularities (later confirmed by Hering in 1900 and Rothberger and Winterberg in 1910)

The clinical application of such observations was the assumption that impaired cardiac function caused by myocardial disease and often associated with distension of its chambers was the chief cause of such arrhythmias Such views can be found in papers by Fothergill (1870 1872) Nothnagel (1876 rather guarded inasmuch as he enumerated a long list of conditions including many other than cardiac disease) Riegel (1877) Rosenstein (1877) Dehio (1893 for those instances in which atropine failed to abolish arrhythmias the disturbance was located in the automatic mechanism of the heart itself) In 1893 Mackenzie regarded the bigeminal pulse as evidence of a jaded heart and always associated with evidence of failure of heart power —a view which he was to change radically in the course of the next twenty years As late as 1898 Riegel who had extensively studied cardiac arrhythmias wrote that from a clinical point of view the commonest cause of all irregularities of heart action were diseases of the myocardium The disproportion between cardiac energy and the resistance to be overcome by the heart beat was stressed as an important factor in the production of extrasystoles by Vaquez in 1911 Nefedoff in a paper published in 1913 from Vaquez s Institute emphasized that extrasystoles are a sign that the heart is no longer capable of overcoming the peripheral resistance and that extrasystoles sont d une frequence extrême au cours ou à l approche de l insuffisance cardiaque from which he drew the corresponding conclusions about their prognostic significance

It may be mentioned parenthetically that more recently the part played in the production of ectopic arrhythmias by mechanical distension and stretching has again been considered Fredericq (1924) found in the isolated turtle s heart a decrease in chronaxie with increased mechanical distension of the muscle fibres Bard (1925) attributed the occurrence of ventricular as well as of auricular extrasystoles to distension and intracardiac changes in pressure and Scherf Scharf and Goklen (1949) found a pronounced effect upon ectopic arrhythmias produced by the topical application of aconitine on stretching auricular muscle

An interesting interlude is provided by the attempts to explain the intermittent pulse by the assumption of hemisystole that is the contraction of only one half of the heart This idea seems first to have been put forward by Charcelay in 1838 He noticed the absence of a carotid pulse with every other beat while the jugular pulse was present in every beat with others only the carotid pulse was noted without the jugular one He attributed this to dyschronisme between the two ventricles and concluded En consequence qui dit systole du ventricule droit dit pulsation jugulaire qui dit systole ventriculaire gauche dit pulsation carotidienne But the main protagonist of this view was Leyden who on the strength of observations in one case (1868) attributed the second beat of a *bigeminus* to the isolated contraction of the right ventricle and on the strength of two additional cases of this kind drew far reaching conclusions about the underlying mechanism (1875) In cases of advanced mitral incompetence the regurgitating blood was—in his opinion—ejected into the pulmonary capillaries where it met the blood stream of the pulmonary artery and these two streams cancelled one another The result he believed to be that only with every second beat was the filling of the left heart adequate for producing a pulse The patent impossibilities of such an explanation were exposed almost immediately by Bozzolo (1876) mit mehr Witz and Grunden als Hoflichkeit and Complimenten (to quote Malbranc s words about this strongly worded paper of Bozzolo) All the same the number of leading members of the profession at the time who accepted this view is amazing they include Gerhardt (1876) Malbranc (1877) who coined the term *Hemisystolia cordis* and accepted it in a modified form Rosenstein (1876) Friedreich (1878) and as late as 1908 it was not only still accepted by Kraus and Nicolai but re iterated by Leyden (and Bassenge)—a remarkable record for an eminent man to adhere for forty years to a patently erroneous view in the face

of numerous publications which refuted it on experimental or clinical grounds Bozzolo (1876) Riegel and Lachmann (1880) Mackenzie (1893 p 110) Frank and Voit (1900) Hering (1908) amongst them

Other unusual explanations of cardiac irregularities were based on teleological considerations In a way Hodgson s view (1815) belongs to this group He had observed double contractions of the heart with one pulse at the wrist in contraction of the left auriculo ventricular opening this he attributed to two contractions of the auricle to one of the ventricle these being necessary in order to drive sufficient blood through the stenosed ostium He considered this of diagnostic significance The double pulse at the heart may therefore I conceive be regarded as characteristic of contraction of the communication between the auricle and ventricle and in the absence of this double pulse violent action of the heart accompanied by a small pulse in the arteries may be considered as the diagnosis of obstruction at the orifice of the aorta This seems an early attempt to use changes of rhythm for diagnostic purposes in valvular disease Hodgson apparently noticed the greater incidence of arrhythmias in mitral as compared with aortic valvular disease

Fothergill (1870) accounts for the longer diastolic intervals in cardiac arrhythmias thus The wearied muscular fibres claim every now and again and often very rhythmically a longer diastole and fatigue asserts itself in a longer sleep however the irritant may goad The heart s brief fitful sleep has its longer and shorter periods of rest according to its necessities as has the organism under weariness Handford (1888) held that linked beats (what we would now call extrasystoles) had the function to effect a complete emptying of the ventricles which one contraction was incapable to achieve Nicolai and Plesch (1909) had similar views regarding extrasystoles occurring in complete A V block their function consisted in increasing the ventricular rate and minute volume after exercise because the normal mechanism was absent owing to the block As recently as 1949 a similar observation made in a case of sinus bradycardia with A V escaped beats was termed Lebensrettende Extrasystolen by Katsch and in flowery neo vitalistic language hailed as a contribution to New Ways of Thought in Medicine

To revert after this digression to the historical development of our conceptions on cardiac arrhythmias Until almost the end of last century papers on intermittent pulse were mainly descriptive and inferences about the clinical significance largely speculative Attempts at some classification other than purely descriptive were occasionally made Some of the work on *pulsus bigeminus* and *alternans* was of this nature (*see* above in this chapter also chapters on Coupling and on Alternans) Another instance is the introduction by Sommerbrodt (1877) of the term allorhythmia for some periodically recurring alteration in the strength or duration of the individual pulses which in turn alternates more or less frequently with normal rhythm or entirely arrhythmic pulses and which usually was a transient phenomenon (p 396) This term coined for arrhythmias in which a dominant rhythm could be discerned proved subsequently helpful for distinguishing the complete arrhythmia of auricular fibrillation from other kinds of irregular heart action Baumgarten (1888) distinguished between a deficient pulse during which no heart sounds were audible and an intermittent pulse also called *pulsus pseudodeficiens* in which variety the heart contracted but the pulse thus produced was too weak to become palpable at the wrist In retrospect this may have been the distinction between dropped beats and extrasystoles (This distinction may have been implied in the paper by Willis *see* above and in Laennec s (1819) differentiation between intermittences and fausses intermittences the latter were tres facile a distinguer par le cylindre d avec *arrets* ou *hesitations* du coeur)

Progress became possible with a better understanding of the physiology of irregular heart action in particular of the significance of the refractory period and with the development by Mackenzie in 1892 of a convenient method for recording in man auricular as well as ventricular activity

The question as to the cause of the heart s rhythmical action has aroused man s curiosity for centuries That it greatly occupied Leonardo da Vinci is evident from his writings of which the following may be quoted (after Keele)

And which part of the heart it is which is the cause of the movement and whether it is inside or outside the heart

Leonardo seems to have been the first to have thought of a myogenic and what is more

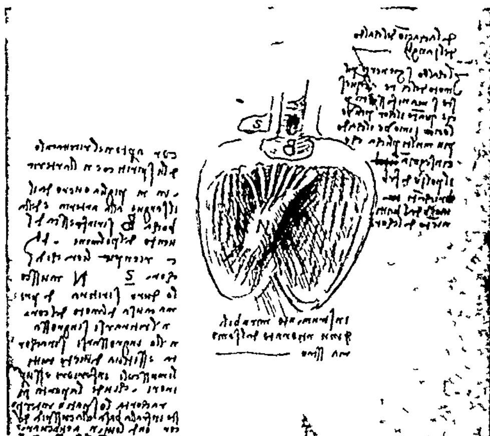


Fig 5 —Leonardo da Vinci Dell Anatomia Fogli B Royal Library Windsor An early drawing of the left heart showing the first cause of the movement of the heart considered by Leonardo to lie in the papillary muscle N From K D Keele (1952) *Leonardo da Vinci on Movement of the Heart and Blood* Harvey & Blythe London

important in the context of this book of an automatic origin In an early drawing of the left ventricle he drew a large papillary muscle labelled it N and wrote

N hard muscle contracts itself and is the first cause of the movement of the heart (*See* Fig 5)

Of the heart This moves on its own and does not stop unless for ever

This is a clear conception of an automatic origin of the heart beat but for the name

Leonardo did however also consider the reversive nerves (vagi) as an alternative cause of the heart s movement and although these notes give evidence of an early origin (*ca* 1500 Keele personal communication) Keele did not find this subject mentioned again and assumes that Leonardo never found satisfactory answers to these questions

The first to pronounce the heart s action automatic also in name seems to have been Borelli In his *De motu animalium* the first edition of which was published in 1681 two years after his d ath he stated And these unless I am mistaken are sufficient to persuade me that the movement of the heart can be carried out by natural instinct nay by organic necessity and moves automatically

Nevertheless it will not be superfluous to see whether there are reasons for doubt or whether the heart is moved not merely by natural mechanical necessity but by that same animal faculty by which all the other muscles are moved (*See* Appendix O)

These words merit to be quoted not only because of the intrinsic interest of this statement—and the conception of automatic will be shown to be of considerable importance in the context of this book—but also because of the historical importance of Borelli qui a divers points de vue doit etre considere comme le point de depart de la route scientifique sur laquelle se recontreront au XIX^{e} siècle J Muller R Maver H Helmholtz et depuis Ch Ludwig et J Marey (M del Gaizo 1909)

Marey is universally credited with the clear formulation of the laws governing rhythmical and arrhythmical action of the heart In no way does it detract from Marey s great achievement to point out that more than a hundred years before Felice Fontana originated the conception of what Marey termed refractory period (Hoff) Fontana suggested that the relaxation of a muscle during prolonged stimulation is due to exhaustion of its store of irritability by the very act of contraction and applied these arguments to the heart here the stimulus (believed at that time to be the presence of blood in the chambers) was constant but though the heart was continually stimulated chemically as well as mechanically it relaxed after a time owing to exhaustion of irritability of the heart muscle the heart rate therefore depended on the rate with which the heart gained and lost its irritability Fontana should therefore be credited with the discovery of the refractory period (Hoff) The first to differentiate between what is now called absolute and relative refractory period seems to have been Schiff (1850) who found that the length of the diastole could be shortened by a modified and stronger stimulus applied at a time when the heart was not vet responsive to the normal stimulus These ideas remained unknown to the majority of physiologists until Marey showed that the phase of absolute non responsiveness depended on the intensity of the stimulus and on the temperature and that the forced beat was followed by a longer interval which he termed compensatory pause as in his opinion it compensated the heart for the increased expenditure of energy incurred by the two preceding contractions the forced beat and the preceding normal contraction (Marey 1876)

It was not until Engelmann s work (1895) on the mechanism underlying the compensatory pause that the understanding of the physiology of these arrhythmias had reached a stage which became applicable to clinical work He showed in experiments on the suspended frog s heart that the interval between the last normal beat preceding an extrasystole —which term he first used in 1895—and the first post extrasystolic beat equals in length the length of two normal cycles (confirming an observation of Knoll in 1872), and found the explanation in the fact that the forced beat originated independent of and did not affect the normal pacemaker The next normal impulse reaches the ventricle at a time when it is in the refractory period from the extrasystole and therefore fails to produce a contraction The next ventricular contraction has to await the following normal auricular impulse therefore the interval between the extrasystole and the following beat is prolonged by an amount which makes the pause compensatory in that the original rhythm is resumed with the first post extrasystolic beat and thus preserved in spite of the occurrence of the extrasystole The same mechanism obtains in the case of several extrasystoles in succession Similar conditions were observed with extrasystoles originating in parts other than the ventricles with the important difference that in the case of auricular extrasystoles the post extrasystolic pause usually was shorter than compensatory and with extrasystoles

originating from the *sinus venosus* no lengthening of the post-extrasystolic interval occurred These laws were soon found to be valid also in the mammalian heart (Cushny and Matthews 1897)

The application of these physiological discoveries to clinical cases is due to Cushny and to Wenckebach who in the same year 1899 independently put forward the view that in many instances the intermittent pulse was due to extrasystoles Both these workers arrived at these conclusions by accurate measurements of arterial tracings only and by noticing the similarity in the time relations between the sequence of beats in the radial pulse in man and that of the contractions of the heart as the result of extrasystoles in the experimental animals The conclusive proof was furnished by Mackenzie s graphic records of the venous pulse which made accurate recording of auricular in addition to ventricular activity in man possible and applicable on a large scale These views were confirmed experimentally by Hering (1900) His statement that a complete absence of lengthening of the post extra systolic interval always pointed to the origin of the extrasystole in the large veins was cor rected from his own Institute by Pan (1903) who showed that in certain cases ventricular extrasystoles may occur in man without producing any change in the sequence of normal beats He thus confirmed the experimental findings of Trendelenburg (1903) and described what are now called interpolated ventricular extrasystoles In the same year Wenckebach summarized the knowledge then available and for the first time described the arrhythmias not as disturbances of the pulse but as an expression of well defined disturbances of cardiac function The discovery and recognition of the function of the specialized conducting system in the heart and the invention by Einthoven of the string galvanometer were the final steps leading up to present day conceptions of extrasystolic (and other) arrhythmias The first electrocardiogram of extrasystoles was recorded in 1906 by Einthoven who noticed the abnormal spread of the excitation wave of the premature contraction

SUMMARY

The starting point in this review of the historical development of our conceptions about certain arrhythmias is the art of feeling the pulse as it was practised in ancient China It was believed that the site and nature of all diseases could be diagnosed from the pulse alone and various kinds of irregular pulse were described some of which are briefly dis cussed In the second century A D Galen taught that with certain differences in degree the intermittent pulse had on the whole a very ominous significance often indicating impending death Galen s writings are briefly reviewed as far as they are relevant to the assessment of the significance of the irregular pulse His views held sway until the end of the last and to a certain extent even into the present century

In the sixteenth seventeenth and eighteenth centuries Galen s views were still generally accepted mainly in their original form though interpreted and modified according to individual observations This is illustrated by the writings of Diversus Ballonius Fienus Lower Floyer Friedrich Hoffmann Dissenting opinions are known to have been put forward from the sixteenth century onwards for example Struthius Johann Weyer Schenck a Grafenberg Amatus Lusitanus Willis Lancisi E A Nicolai Senac Heberden Mor gagni Stoll Skoda Solano de Lucque claimed that certain types of irregular pulse indi cated with certainty various approaching crises and had an extremely good prognosis The views of the authors mentioned are discussed and illustrated by quotations

In spite of dissenting views the ominous significance of the intermittent pulse was the current view in the second half of the nineteenth century this is exemplified by Fothergill s writings During that period the role played by the cardiac nerves and by disproportion between the strength of the heart and the amount of work it had to perform attracted great attention as being important factors in the causation of arrhythmias It is pointed out that

until the second half of the nineteenth century papers on the irregular heart action were mainly descriptive though some attempts at classification were made these are briefly reviewed The prognostic significance of bigeminal heart action became obscured by Traube s identification of *pulsus bigeminus* with *pulsus alternans* Some unusual views about cardiac irregularities of that period including that of hemisystole are briefly discussed The importance of Marey s work for the understanding of arrhythmias is stressed although the credit for the first description of what Marey called refractory period should be given to Fontana who originated this conception nearly a hundred years before Marey The modern views about the mechanism underlying extrasystolic arrhythmias are based on Engelmann s work on the frog s heart the essence of which is briefly reviewed Its application to clinical work is due to the independent work of Cushny and of Wenckebach who recognized that in many instances the intermittent pulse is due to extrasystoles The importance of the clinical work of Mackenzie and of the experimental investigations of Hering is briefly mentioned The recognition of the function of the specialized conducting system in the heart and the invention by Einthoven of the string galvanometer are shown to be the final steps leading up to present day conceptions of extrasystolic and other arrhythmias

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APPENDIX

A Rufus

Le pouls est appele *dicrote* lorsque l artère après avoir accompli une grande diastole en fait une plus petite Ce pouls se montre chez les individus bien portants à la suite de courses d exercises gymnastiques ou de tout autre effort brusque chez les malades il se rencontre particuli rement à la periode d augment dans les fièvres Le pouls est appele *caprisant* quant a un grand battement succ de immediatement un petit battement en sorte que l artère semble se reprendre pour une nouvelle diastole avant d avoir enti rement acheve la systole Ce pouls est surtout observe dans les affections de la poitrine

B Galen

9 294 Est periculosissimus hic quoque omnium intermittens Haec fit ubi distensionem interpellat quies cujus multae sunt species omnes illae quidem periculosae sed inter se secundum magis aut minus dissidentes Ubi enim vehementior secundus motus fit priore commodius est ubi languidior periculosus

9 544 Mors porro repentina ex intermittentibus evenit pulsibus quo modo ex apoplexia extinguitur enim in utrisque caliditas quae in corde est respiratione privata

9 283 Quamobrem intermittentes pulsus minus habent senes quam juvenes perniciales mox pueri ab illis quod (quia quum concotrice facultate sint validissima tum corpore mollissimo atque facile perspirabili) concoquant digerantque per halitam intemperies inaequales copiamque humorum et crassitudinem Quare etiam in minus periculum veniunt quam juvenes quum pulsus intermittunt duobus nominibus nam tum

quod facultate quae pulsibus praesidet imbecilliore quam juvenes sint ut a minoribus causis sicut senes superentur proclivius tum quod concoctrice firmiore ut facile offensae corrigantur

8 515 Utriusque porro horum proportionem non servantis et servantis is qui habet proportionem pulsus commune est genus Atque proportionem habens quidem unus et indivisus manet proportionem non servantis tres sunt omnes differentiae pararhythmus heterorhythmus ecrhythmus Qualis vero quisque sit exemplo disces Suus est cuique aetati naturalis pulsus qui jam de his rhythmum servat eurhythmus vocatur qui labefactat arhythmus Atque labefactans interim rhythmum vicinae aetatis mutuatur qui pararhythmus interim cujusvis alterius ac heterorhythmus hic appellatur at qui rhythmum nullius aetatis retinet hic ecrhythmus (Similar more extensive classification in 19 409)

9 471 Ac exiguam quidem eversionem indicant pulsus pararhythmi majorem heterorhythmi maximam ecrhythmi

19 410 seq Dicrotus est pulsus quum remissio quae videtur arteriae non perfecta obitur sed cunctatio pro subductionibus aut inhibiti spiritus quantitate dein resusio perfecta debitae fit contractionis

Intermittens pulsus est quum in systolis et diastolis abeundis pulsus unius arteria tempus omittit Quid am ita intermittens est pulsus in quo non ad duos tantum sed ad tres vel etiam plures ictus diastolen unam vel duas vel plures relinquit arteria

Intercidens pulsus est quum inter duos ictus qui ordine proprio concitantur inde quidam ictus medius intercidit

Deficiens pulsus dicitur in quo non ad duos tantum arteria sed ad tres etiam et ad plures ictus immobilis perseverat Alii hunc in modum Deficiens est quia magnitudine incipiens ac vehementia magis ac magis subinde minuitur talisque quoad ullam habeat magnitudinem myurus vocitatur

Caprisans pulsus est ubi arteria quum se distendisse apparuerit nec fuerit omnino distenta ad alium perculsum prius quam systoles visionem praebeat praecipitantius transilit secundo autem fuit percussio facta vehementior

19 640 Quid differt caprizans a dicroto? Quod caprizans quidem in una systole motus effi it diversos quemadmodum subsultans capra pedibus salit in aerem Dicrotus vero bis in eodem pulsat

C **Montagnana**

Sed ista ẽ ro formalis bispulsantis Igit appet in hº iuveculo cu tremulo motu cordis pulsus bispulsas qd erat dclarãdu (Sed ista est ratio formalis pulsus bispulsantis Igitur apparet in hoc juveculo cum tremulo motu cordis pulsus bispulsans quod erat declarandum)

D **Diversus**

alteru est quod in his pulsus quandoque accedit intermittens qui si supra unicam intermittat pulsationem magnu periculum minatur significatque syncope hanc instare quae intermissio sicuti & illa praefocatio non aliunde generatur quam ex illa sanguinis coalescentis copia obstruentisque ac gravantis vasa illa & partes internas

E **Ballonius**

Nunc ad intermissionem revertamur Aliquando intermittit pulsus tantum quantum temporis esse possit in alia promovenda pulsatione aliquando intermittis diutius & per duorum pulsuum tempus Hoc posterius funestum est nec ab eo quisquam convaluit Per tempus vero totum unius pulsus aut paulo diutius intermissionem factam saepe in plerisque qui convaluerint observavit Galenus praesertim si iam affecta aetate aut praecipitati senes essent

F **Fienus**

Intermittens singularis est pulsus inaequalis in quo diastole non est continua sed interrumpitur aliqua quiete aut cessatiuncula Dico (intermittens singularis) ad distinctionem intermittentis systematici nam in intermittente singulari est cessatio & intermissio motus in una diastole ac in una pulsatione & intermissio unius portiunculae in ipsa diastole in intermittente vero systematico inter multas diastoles seu inter multas pulsationes intermittitur una diastole integra Intermittens ergo singularis est pulsus inaequalitate singulari in una pulsatione sub eodem digito secundum celeritatem nam ubi est quies ibi nam est aequalis celeritas Hic intermittens etiam oritur a facultate gravata & simul valde debili adeo ut non possit facere unam diastolen integram quin debeat intermedio tempore cessare quapropter peior est intermittens singularis impare citato Peior est etiam intermittens singularis intermittente systematico quia maior debilitas est non posse unum motum seu unam pulsationem facere sine intermedia quiete quam non posse facere multas Intermittens hic non tantum gravatam ac debilem indicat facultatem sed etiam usum auctum nam si non adesset usus auctus qui stimularet & cogeret naturam ad perficiendum istam pulsationem interruptam natura cum illa incipiente quiete cessaret in totum & non perficeret integram diastolem sed quod post interceptam quietem non esset fit quia usus auctus naturam nimis stimulat et irritet ad hoc faciendum Intermittens singularis est valde malus & proximam solet indicare mortem patet ergo quod hic pulsus in una diastole bisferiat

Capricans est species huius intermittentis iam dicti & fit ab eadem causa differt tamen in eo quod in intermittente iam dicto sit solum inaequalitas secundum unam differentiam nempe secundum celeritatem in capricante vero est inaequalitas & secundum celeritatem & secundum vehementiam nam bisferit & habet quietem & sic in eo est inaequalitas secundum celeritatem sed posterior pars diastoles quae sequitur cessationem est vehementior anteriore seu parte diastoles cessationem praecedente Est hic pulsus valde pravus sicut omnes intermittentes & facultatis indicat debilitatem et oppressionem sed tamen per hoc indicat adhuc aliquam bonitatem quod posterior pars diastoles sit vehementior priore per quod indicatur naturam valde gravari & opprimi & cum causa morbifica confligtari sed eam adhuc posse fieri superiorem

Dicrotus est etiam pulsus in una diastole seu pulsatione bisferiens in quo motus retrocedit & redit &

diastole à systole quasi retrahitur & hic est etiam pulsus inaequalis in una pulsatione sub uno digito habens intermediam quietem Inter hos pulsus est exigua differentia & sunt potius differentiae rationales quam sensuales inventae potius per speculationem quam quod ipsas sensus distinguere posset Conveniunt in eo quod sint omnes pulsus bisferientes habentes diastolem interruptam quieta media

G Hoffmann

Inaequalis vero arteriarum pulsatio sive mox magna mox parva mox celeris mox debilis intermittens quoque fit quando liber sanguinis transitus per vasa coronaria vel etiam ventriculos cordis a quodam obstaculo impeditur ac vel sanguis grumefactus crassus in vasis coronariis vel fibrosum aut polyposum concrementum in auriculis vel cavitatibus ventriculorum vel vasorum cordis haeret vel etiam fit quando sanguis crassus & copiosus celeriter ad cor truditur & systolen ejus ad tempus opprimit

H Struthius

Dum essem apud imperatorem Thurcorum Soltanum Suleimanum Sachum comperi militem quendam Thurcicum in acuta febri dicrotum semper obtinuisse pulsum qui post elapsam aegritudinem nihilo fuit immutatus cum certis vere convalescentis corporis indicijs unde coniecturam accepi natura insitu fuisse ipsi huius modi pulsum Plurimum igitur expedit homines sanos cum medicis saepe conversari quibus in morbo se sint concredituri Facile enim memoria retinere potest medicus familiaris qualis in sanitate fuerat pulsus heri aut amici sui in morbo iam decumbentis quem quantum sit mutatus probe deprehendet Quod si vero reperias pulsus malos & horrendos apud aegrotum quem non noueras & cuius arteriam antea non tetigisti priusquam aegrotaret meminens istius regulae Si ex omnibus alijs indicijs morbus appareat sine periculo pulsum terrificum ex natura adesse sciendum est aut prorsus ante aegrotationem eum fuisse propter aliquam causam evidentem

I Weyer

(917) Rutgerus a Randwick nobilis aetate plus quam quinquagenarius temperamento biliosus incidit in febrem summae malignitatis Pulsatio arteriarum deprehendebatur valde inaequalis & inordinata usque ad septimum diem quo percipi coepit Intermittens cui quadam motionis vicissitudine caprizans succedebat Sed hic nondum arripui desperationis ansam licet haudquaquam me lateret Galeni de hoc signo judicium prorsus formidabile

(918 §5) Septima rediens mane in acerbo consanguineorum astantiumque lu tu citra ullam dilationem digitis carpo admotis pulsum percipio intermittentem tertia quaque pulsatione Qui primo quidem contactu terrorem incutit at examinatis interea caeterorum accidentium praesagiis indeque certa convalescentiae spe data qui quid discriminis portendebat variata illa cordis & arteriarum motio id totum retuli ad acerrimam naturae cum vi morbi concertationem

(920 §9) Verbi gratia Statuamus aegritudinis causam aut parem esse naturae aut imparem Par si fuerit non apparebit conversio vel ad salutem vel mortem quia mutationis omnis proprietas consistit in unius praedominio Si igitur impar tum aut morbus vincet aut natura Si natura evadit aeger sin minus morietur Mortem enim invehit defectus naturae ex superantia causae morbificae Iam pulsationis omnis continuatio significat facultatis vitalis robur defectio autem ejus imbecillitatem Itaque si binam pulsationem exhibuerit tactus bini numerabuntur gradus roboris si una intermissio unus gradus morbi At unus gradus minime exsuperare potest duos in actionis ordine Unde pulsus licet tertia quaque motione intermittens non arguit imminentis mortis certitudinem atque multo sane minus ille qui decem aut viginti dilatationum & contractionum repetitiones tantum sequitur

(921 §11) Ea mihi narravit filius meus Henricus Wierus philosophiae & medicinae Doctor qui propter assiduas studiorum labores Bononiae incidebat in similem palpitationis Cardiacae affectum cum pulsu inordinate caprizante & saepius intermittente sed venae sectione virtus lege rite observata assumptis quoque iis quae ex artis nostrae praeceptis conducibilia judicabat integram sanitatem ex singulari Dei gratia est consecutus

J Horst

Etsi nulla in re vulgus Medicum magis admiratur & extollit quam in futuram praedictione cum nihil in arte Medica mirabilius videatur quam per certa signa salutis atq mortis eventum praedicere non tamen temere ed caute procedendum esse saepius Hipp monet propterea quod in acutis subitae sint mutationes ubi merito notanda venit observatio Wieri de curatione febris malignae in qua de pulsus intermittentis praesagio disputatur cujus verba sunt haec (follows a quotation of the above observation of Weyer)

K Schenck

Cum ante triennium forte proprium pulsum attentius explorassem animadverti eum intermittentem esse Nam interdum post quartum aut quintum interdum post septimum aut nonum interdum post duodecimum aut decimum tertium ictum intermittebat Quo symptomate cognito vehementer equidem perturbabat Non enim ignorabam quae Galenus & alii medici de pulsu intermittente deque eius causis senserant Recreabat tamen me quod in actione nulla vel vitali vel naturali evidentem lesionem perciperem & quod iam aetas mea ad senium vergeret in quo minus noxiam hanc pulsus intermissionem expertum esset At vero ne saluti meae deessem in victu aliquanto cautior esse coepi & ea fugi quae vel obstructiones in venis cordis proximis efficere vel robur cordis convellere atque labefactare possent Itaque temporis progressu haec pulsus immutatio quae fere integrum annum durarat emendata et correcta est

L Amatus

Jacobus Basilius nobilis Ragusaeus morbo gallico & oculoru suffusione laboraret Caeterum hic cum sit quadraginta quinque annorum morbis huius successu ut ego ad eum accedens deprehendi pulsus intermissionem habebat singularis nanque quatuor vel quinque pulsationibus arteria deficiebat remorabatur

& detinebatur & temporum duorum ictuum sive duarum pulsationu immobilis manebat signum ut a me ijs in Centurijs audistis malum praesertim in febribus continuis ut Curatione quadragesima tertiae Centuriae perample sum persecutus & si recte teneo ex Galeno dixi intermittentes pulsus in iuvenibus periculosiores habentur dein in pueris caeteris minus periculosi in senibus Caeterum cum intermissio pul us huic evenerit ob arteriam a crassis & malis succis compressam non vero ob vitalis facultatis imbecil litatem non difficulter fuit eum brevi liberare ad causam unde mala affectio originem trahebat attendendo Cor autem tunc roboravimus & humores ab eo retraximus quos postea attenuavimus incidimus & postea purgavimus unde pulsus ex heterorhythmo hoc est multu a proportione & consonantia distante para rhythmus & postea eurhythmus id est consonus est factus & aegrotus ipse ex toto sanus

M Lancisi

Et quidem primo quantum spectat ad pulsuum vitia etiamsi apud aliquos inaequalitas atque intermit tentia tanti fiat ut inde Gal subitam mortem Antipatro praedixerit nos tamen signum ho non solum in pueris & senibus ut idem asservit Galenus sed etiam in juvenibus & robustis frequenter nullo modo funestum observavimu cum scilicet ex levi connutritio organorum vitio vel ex hypochondriorum irritatione procedit cujus forsitan indolis extitit intermittentia pulsus illius Oeconomi quem ipse Galenus tanquam sanum ad consueta nego ia ingenue remisit Etenim si sola pulsus intermittentia hominem bene caeteroquin valentem detineat adeo optimos Medicos a subitaneae mortis praesagio dehortatur ut potius eos in spem adducat leve illud malum antequam gravius evaserit opportuna medela fore tollendum Hujus veritatis ex me met ipso experimentum promam qui cum tria ante lustra pertinaci mihique sensibili cordis contrac tione indeque orta pulsus intermittentia ex hypochondriorum consensu per sexennium laboraverim plus aliis quam mihi officiosus & cautus usu tandem rhabarbari chalybis & juris viperati perfecte convalui Ut igitur intermittentia pulsus improvisae necis certius omen esse possit necesse est ut jungatur omni inaequali tatum generi palpitationi anhelitui aliisqui similibus pectoris passionibus de quibus infra

N Solano

p 88 After re stating Galen s view of the very grave significance of the intermittent pulse he goes on to say that he (Solano) believed this hasta que Dios por su alta è inexcrutable providencia permitiò que yo experimentasse ser muy al contrario las mas vezes como le veras muy presto bastando por aora el que confiesso delante de Dios que las mas vezes con tal pulso observè que se siguieron maravillosas felizidades

p 95 La cantidad tambien siguiendo el mismo sensato rumbo philosoꝭico no sin confusion de muchos sospechè por el espacio de las intermissiones y la experiencia (madre de la verdad) la contesto en la misma forma Adverti pues que quando las intermitencias eran largas ò de mucho espacio era mucha la copia ò causa material que havia que mover y quando breves era po a (The evacuation of the morbid mat rial requires a concentrated effort of Nature just as any other activity necessitating a great effort) En este me persuadia el experimento natural y quotidiano de acà fuera en que vemos y experimentamos todos que para cumplir una accion como de alzar mucho material ò de impeler un grande piedra ò de luchar con otro en que sea menester fuerza mucha è impulso sucesivo ò largo se recoge por gran rato la naturaleza privan dose en el de otras acciones para arrimar todo el esfuerzo y virtud que s divertia en ellas tan solamente a aquella obra y en una carrera se nota que repite el agente los conatos largos suspendiendo toda otra accion hasta la de respirar para con las fuerzas unidas dar mas presto satisfacion à aquel empeño A este modo quando es mucho el material morboso s suspende ò recoge mucho para haciendo mas fuerza poder impelerlo todo y por esto s vè la intermission larga y espaciosa y quando es poca como no es menester tanto impulso y conato con menos tiempo de union de fuerzas y por consiguiente de menor intermission ti ne bastante para mover y exterminar enteramente la causa y asi se experimenta que los conatos son menos vigorosos y las intermissiones mas cortas

(until God in his supreme and ins rutable providence allowed that my experience was nearly always to the contrary as you will see presently suffice it for the moment that I confess before God that with such pulse nearly always followed admirable recoveries

The quantity too following the same judi ious philosophical pro edure and not without the conster nation of many I divined by the interval of the intermissions and exp rience (mother of truth) confirmed it in the same manner Thus I noticed that when the intermissions were great or with long intervals the quantity or material cause which had to be moved was large and if they were short it was small

In this I was p rsuaded by the natural and daily exp rience in real life in which we se and we all exper ience that in order to complete an action such as lift much material or propel a large stone or fight with someone in which much strength is necessary and a sustained or heavy pressure Nature retrenches on a large scale depriving herself of other activities in order to concentrate all her strength and vigour which is diverted to them exclusively on that work and one furth r observes without delay that this principle repeats the great efforts susp nding every other activity even breathing so that the united forces bring such task more quickly to a satisfactory conclusion In this way when there is much morbid material much is suspended or economized for propelling everything with more force and for this reason one sees a great and long intermission and if there is little (morbid material) sin e there is no need for so much pressure and effort with less time of union of forces and therefore with shorter intermission there is enough (strength) to move it and entirely to exterminate the cause and thus one experiences that the efforts are less vigorous and the intermissions shorter) (Our translation)

O Borelli

Et haec ni fallor satis suadent motum cordis fieri posse naturali instinctu seu necessitate organica non secus ac automa movetur

Nihilominus non erit supervacaneum videre an adsint rationes dubitandi utrum cordis motus fieri possit non a mera naturali mechanica necessitate sed ab eadem facultate a qua omnes alij musculi moventur

CHAPTER II

DESCRIPTION OF THE VARIOUS TYPES OF EXTRASYSTOLES

VENTRICULAR EXTRASYSTOLES

Ventricular extrasystoles originating in a ventricle those arising in the stem of the bundle of His should be included but in view of certain peculiarities of this variety they are discussed in a separate section (*see* p 95)

The Nature of the Disturbance of Rhythm

Fig 6 illustrates diagrammatically the disturbances of rhythm produced by ventricular extrasystoles



Fig 6 —Diagram illustrating the nature of the disturbance of rhythm caused by a ventricular extrasystole The figures indicate intervals in hundredths of a second (except the top row which indicates consecutive numbers of S–A impulses)

It shows three normal beats followed by a ventricular extrasystole The ectopic stimulus spreads over both ventricles resulting in a premature contraction and also is conducted in a retrograde direction over a certain distance but in the human heart usually fails to reach the sino auricular node as it is blocked below or in the atrio ventricular node In the majority of cases the next normal stimulus occurs at a time when the conducting system still is in the refractory period of the extrasystole and not being conducted to the ventricles fails to yield a contraction The following normal stimulus (No 5 of Fig 6) reaches the ventricles in the normal way Thus the sinus and auricular rhythms are undisturbed by the ventricular extrasystole one ventricular contraction occurred prematurely but as the *interval between the extrasystole and the last preceding normal beat plus the post extra* systolic interval equal the interval between two normal beats the original rhythm is preserved and resumed with the post extrasystolic beat

We propose to use the following terminology dominant rhythm in order to describe the underlying or prevailing rhythm which is interfered with by the extrasystoles coupling to denote the interval between the beginning of the ventricular complex of the last beat preceding the extrasystole and the beginning of the extrasystole post extrasystolic interval is called the interval between the extrasystole and the first post extrasystolic beat When applicable the term premature beat is sometimes used instead of extrasystole This terminology seems to us preferable to the one used by Lewis who called the cycles of the dominant rhythm preceding an extrasystole initial cycles the coupling extrasystolic or forced cycle according to whether the beat which ends it

is spontaneous or forced by stimulation the post extrasystolic cycle returning cycle and the subsequent ones restored cycles "

With a given and constant sinus rate the post extrasystolic interval (the compensatory pause) becomes longer as the interval between the extrasystole and the last preceding normal beat (the coupling) becomes shorter (Marey Cushny and Matthews)

It has been pointed out by Engelmann that if more than one ventricular extrasystole occur the interval between the first extrasystole and the last preceding normal beat plus the interval between the first extrasystole and the first normal beat following the series of extrasystoles equals a multiple of the normal period If two extrasystoles follow one another at a short interval they usually replace only one normal beat

These rules are valid only if the normal rhythm is entirely regular and even if this is the case the post extrasystolic intervals often fall a little short of being fully compensatory since the first post extrasystolic normal beat is conducted slightly faster to the ventricles than the other beats (Engelmann) This observation was confirmed in man by Wenckebach

The Electrocardiogram

General Features

In the electrocardiogram the typical features of ventricular extrasystoles are premature ventricular complexes of abnormal shape which are not preceded by P waves

The initial deflection or QRS group of a ventricular extrasystole is usually either higher or lower as well as wider than those of the sinus beats and commonly slurred and notched The final deflection or T wave while showing many variations usually is directed opposite to the main deflection of the QRS group but exceptions occur An RS T segment often is missing and when present is displaced in the direction of the T wave

These features recall those encountered in bundle branch block and the resemblance is so close that if the record of one individual extrasystole is cut out from a tracing it can hardly be distinguished from the ventricular complex of a case of bundle branch block Nor is this a coincidence In both conditions the features of the electrocardiogram are due to the fact that one ventricle is activated earlier than the other In the case of ventricular extrasystoles that ventricle is first activated in which the extrasystole originates and until the impulse has reached the other ventricle the action potentials of the ventricle activated first are unopposed by those of the other ventricle higher deflections are thus recorded The abnormal direction of the spread of the excitation (depolarization) wave and its slower rate of conduction account for the abnormal direction and greater width of the QRS groups respectively and the abnormal sequence of the subsequent repolarization is responsible for the abnormal T waves It follows that the features in the electrocardiogram of a ventricular extrasystole will become more abnormal the more distal in the conducting system the site of origin of the extrasystole if an extrasystole originates close to the bifurcation there will be only slight changes and if the site of impulse is in the stem of the bundle of His that is above the bifurcation the extrasystole will give rise to premature ventricular complexes that appear normal It is also evident that the abnormal width of the QRS group of the ventricular extrasystoles cannot in itself be taken to indicate myocardial disease although exceptionally wide complexes not infrequently are found in patients with structural heart disease (*see* below)

In a large majority of cases of ventricular extrasystoles those of any individual case show in the electrocardiogram a remarkable constancy of form over many years and follow the last preceding normal sinus beat at a constant interval that is show constant coupling For an early paper on this phenomenon *see* Lewis and Silberberg (1911) The significance of these observations is discussed in the chapter on Mechanism

The record reproduced in Fig 7 was obtained from a sixty year old man without any

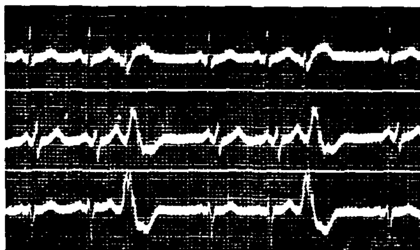


Fig 7—One ventricular extrasystole occurring after every two sinus beats

signs of structural heart disease After every second normal sinus beat a premature ventricular complex of obviously abnormal shape which is not preceded by a P wave is visible a ventricular extrasystole occurred regularly after ever second sinus beat *



Fig 8—Two ventricular extrasystoles occurring in succession in each of the standard leads

* The time marker in all tracings indicates 0·04 second unless otherwise mentioned

The tracings of Fig 8 taken from a forty one year old man do not show any signs of myocardial damage in each of the standard leads two extrasystoles are seen to follow one another replacing one normal beat

Occasionally the QRS complexes are unusually wide thus in Fig 9 they measure 0 18 second The electrocardiogram indicates infarction of the postero lateral (basal) portion of the left ventricle Widening of such degree is not rare in patients with structural heart disease and may occur even if the width of the initial ventricular complexes of the sinus beats is within normal limits Such an electrocardiogram indicates a slowing of the spread of the excitation wave in addition to the other factors already referred to So far as we are

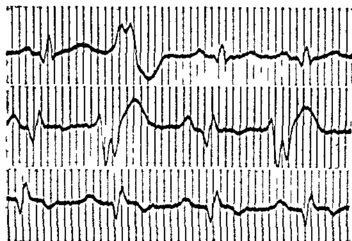


Fig 9 —The standard leads Ventricular extrasystoles with unusually wide initial complexes The sinus beats show the signs of an infarction of the posterior wall Time base 0 05 second

aware it has not yet been determined from which value the increased duration of the QRS complexes of ventricular extrasystoles can be taken to indicate myocardial damage In cases with bundle bundle branch block without any other myocardial lesion the duration of the QRS complexes is 0 12 second or a little less whereas in those associated with myo cardial damage it may greatly exceed this figure

Cases in which the width of the QRS complexes of ventricular extrasystoles is consider ably less than that of the sinus beats are rare In Fig 10a recorded in an eighty year old patient with coronary sclerosis the sinus beats indicate left bundle branch block After the second beat an interpolated (*see* p 85) ventricular extrasystole occurred the QRS com plex of which measures only 0 08 second as compared with the 0 13 second of the sinus beats Fig 10b obtained from another patient illustrates the same phenomenon concerning extrasystoles which were not interpolated Similar cases have been described (Hewlett Wilson and Herrmann) and interpreted as showing beats originating in the interventricular septum with symmetrical spread of the excitation wave over both ventricles The presence of a supernormal phase of recovery resulting in a temporarily improved conduction in the early phases of diastole has also been considered in this connexion (Simon and Langen dorf)



FIG 10—*a*

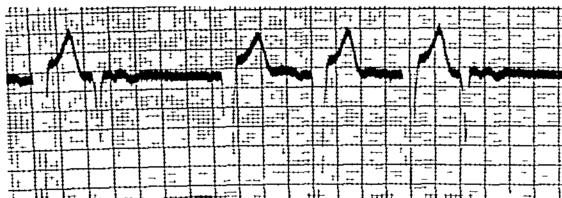


FIG 10—*b*

FIG 10—*a* Lead I One interpolated ventricular extrasystole the initial complex of which measures only 0 08 second as compared with the 0 13 second of those of the sinus beats *b* Lead V 2 Two ventricular extrasystoles the initial complexes of which measure only 0·08 second as compared with the 0 13 second of the sinus beats

Dressler reported an interesting observation made in a case of bundle branch block with occasional ventricular extrasystoles While the presence of bundle branch block masked the electrocardiographic features of myocardial infarction this was revealed by alterations in the S T portions of the extrasystoles A somewhat similar case was described by Simonson *et al* who concluded that the pattern of myocardial infarction or coronary insufficiency may be revealed in ectopic beats in the presence of intraventricular block and that to a certain extent this is independent of the mechanism producing the ectopic beats (For a similar observation in a case of angina pectoris *see* Goldhammer and Scherf Fig 12a)

Alterations by myocardial infarction of the QRS complexes of ventricular extrasystoles are illustrated in Figs 11 and 12 Fig 11 was obtained from a sixty eight year old man with clinical signs of acute coronary occlusion The three standard leads do not show any diagnostic features the deep slurred Q waves and elevated S T segments in lead V 2 and the low R waves and elevated S T junctions in V 5 are diagnostic for an anteroseptal infarct The deep Q waves marked elevation of the S T junctions and distortion of the S T segments in the ventricular extrasystoles as recorded in the chest leads are noteworthy and further significant signs of myocardial infarction Fig 12 was recorded in a sixty nine year old man several weeks after an attack of coronary thrombosis The standard leads and leads



FIG 11 —From above downward the standard leads V 2 V 5 Changes in the QRS complexes of the extrasystoles For further explanation see text

V 1 and V 3 are not diagnostic for a myocardial infarction while the deep QS waves in lead V 5 suggest a lateral infarction The features of the ventricular extrasystole recorded in lead V 3 are noteworthy namely a deep notched QS wave followed by marked elevation of the S T junction pronounced distortion of the S T segment with late inversion of T These *are features commonly seen in lead V 3 in cases of mycardial infarction and it is significant* that in this instance they were displayed by the extrasystole while being absent in the sinus beats in this lead For an analogous observation regarding auricular extrasystoles see p 52 and Fig 35

Single and Multiple Extrasystoles

The frequency with which ventricular extrasystoles occur varies greatly in different individuals and in the same individual at different times If they occur only rarely (inter current bigeminy) it may be difficult for the examining physician to record them in an

electrocardiogram and in order to do so it may be necessary to precipitate their appearance by certain measures (*see* p 336) On the other hand a ventricular extrasystole may follow each beat of the dominant rhythm producing an arrhythmia known as coupled beats or bigeminal rhythm Fig 13 shows an example for its further discussion *see* p 193 One important point may however be anticipated namely that coupled beats or bigeminal heart action may be produced by a variety of quite different mechanisms and that for the sake of clarity such a diagnosis should be qualified and amplified by an indication of the underlying mechanism for example in the above case coupled beats (or bigeminal heart action) due to ventricular extrasystoles

If two extrasystoles follow each normal beat as in Fig 14 the resulting arrhythmia is called trigeminy or trigeminal rhythm In this arrhythmia the two extrasystoles following in succession may have identical shapes in the electrocardiogram or as in Fig 14b they may have different forms By some the term trigeminy is also used to describe an arrhythmia in which one extrasystole regularly follows two normal beats as illustrated in Fig 7 this application of the term trigeminy gives rise to confusion and should be discouraged

The use of the terms bigeminal and trigeminal as outlined above is justified on historical grounds The word bigeminal was originally used at a time when mechanical pulse tracings only were available which in such cases showed two successive elevations often of equal height before the tracing reverted to the base line the idea that such two elevations were produced by a twin contraction was obvious and led to the name In the same way a trigeminal pulse was said to exist when a pulse wave was followed by two more elevations before the record returned to the base line this kind of pulse tracing if caused by an extrasystolic arrhythmia is now known to result from two extrasystoles following a normal beat but does not occur if two normal beats are followed by one extrasystole (*see* also Chapter on Coupling p 193)

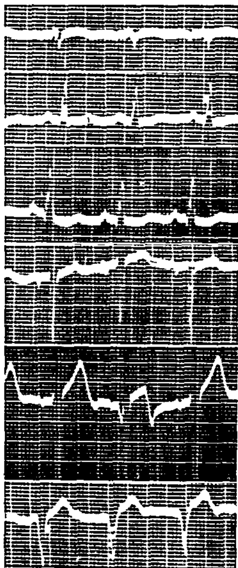


Fig 12 —From above downward the standard leads V 1 V 3 V 5 For further explanation see text

If three extrasystoles follow a beat of supra ventricular origin the resulting arrhythmia is called quadrigeminus an example is provided by Fig 15 It shows auricular fibrillation every beat conducted from the auricles being followed by three ventricular extrasystoles The main deflection of the first extrasystoles is directed downwards the two subsequent

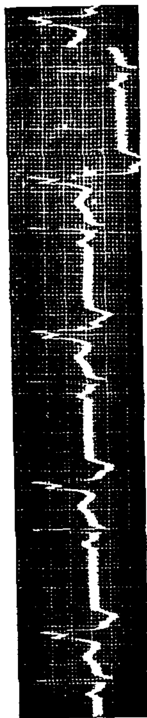


Fig 13 —Continuous ventricular bigeminy owing to one ventricular extra systole occurring after each supraventricular beat



Fig 14—a



Fig 14—b

Fig 14 —Continuous ventricular trigeminy 14a lead 3 14b lead V 2 From two different patients



FIG 15 —Lead 3 Auricular fibrillation and continuous ventricular quadrigeminy



FIG 16—*a* Lead 1 Multiple ventricular extrasystoles with gradual slowing of their rate Time base 0 05 second

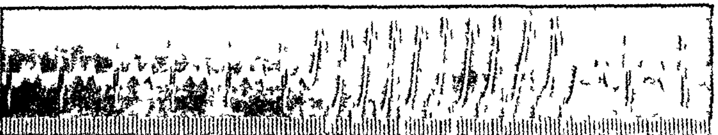


FIG 16—*b* A short period of paroxysmal ventricular tachycardia



FIG 17 —Multiple ventricular extrasystoles showing gradual slowing of their rate The first extrasystole of the dseries *coincides with a sinus beat and the resulting complex* is a combination (or fusion) beat Time base 0 05 secon

ones resemble one another and are mainly directed upwards The individual groups of four beats are identical in their appearance

If successive extrasystoles appear in shorter or longer groups interspersed after several normal beats the term multiple extrasystoles is employed (Lewis) Fig 16a obtained from a case of coronary sinus rhythm provides an example If longer groups of ventricular extrasystoles occur say ten or more the term short ventricular paroxysmal tachycardia would be appropriate (Fig 16b)

If several ventricular extrasystoles follow each other in succession the rate usually remains constant until the chain is suddenly interrupted and sinus rhythm recurs In some instances however the rate gradually slows down as in Fig 16a In Fig 17 which was obtained from a twenty one year old girl otherwise healthy a series of five ventricular extrasystoles was recorded The first of these occurred so late in diastole that it coincided with a normal sino auricular beat so that in the electrocardiogram a transitional complex appeared which was due to a summation of the normal and the extrasystolic complexes The intervals between the successive extrasystoles gradually lengthened A sinus beat which was due to occur during the long post extrasystolic pause failed to appear (*see* below in this section p 43)

The P Wave of the Blocked Sino-auricular Beat

In the great majority of cases the P waves of the blocked auricular impulses occurring during the post extrasystolic interval cannot be identified since the small and slow wave is obscured by the far larger and more rapid notched QRS complexes of the extrasystole Occasionally however if the extrasystoles occur comparatively early in diastole the blocked P wave is visible in the later portions of the QRS complexes or between the QRS complexes and T waves of the extrasystole This is the case in Fig 18 which shows two

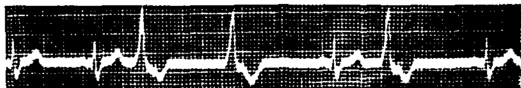


Fig 18 —Lead 2 The blocked P waves of the dominant sinus rhythm are visible in the RS T segments of the extrasystoles

ventricular extrasystoles occurring in succession in the final deflections of which normal P waves can be identified these auricular impulses did not yield ventricular contractions and it therefore follows that the two extrasystoles replaced two normal contractions The ventricular complexes of the conducted sinus beats show abnormal slurring

Post extrasystolic Changes in the Electrocardiogram

The following changes in the electrocardiogram may occur immediately after ventricular extrasystoles

(a) changes in the shape of the ventricular complex of the first post extrasystolic beat or rarely of two or more post extrasystolic beats

(b) occurrence of heterotopic beats

(c) occurrence of abnormal pauses

(a) Alteration of the Features of the First Post-extrasystolic Sinus Beat

Changes in the features of the first post extrasystolic beat are not rare and several types may be distinguished

The commonest variety is that affecting the T waves In some cases such changes go in the direction of normalization that is inverted T waves in lead 1 may become upright in the post extrasystolic beat An example of this is shown in Fig 19 The record obtained from a forty six year old patient with hypertension (B P 220/110) shows the pattern of left ventricular strain (left axis deviation displacement of the RS T segments and direction of the T waves opposite to the main deflection of the QRS complexes) One ventricular extra systole is seen in each lead In lead 1 the T waves were deeply inverted but this wave was



Fig 19 —The three standard leads Marked changes in the form of the T wave of the first post-extrasystolic sinus beat after a ventricular extrasystole

normal in the first post extrasystolic beat in lead 3 the T wave of the post-extrasystolic beat was lower than the T waves of the other beats no changes were observed in lead 2

In other cases changes of the T wave in the reverse direction are observed, namely upright T waves may temporarily become inverted in the first post extrasystolic beat This is shown in Fig 20 taken from a woman aged seventy six a fortnight after a second attack of coronary occlusion The record lead CR 4 shows that the T wave of the first post extrasystolic beat was inverted whereas the T waves of the beats preceding the extrasystoles were upright According to Scherf (1944) inversion of otherwise normal T waves in the first post extrasystolic beat even when it occurs in an otherwise normal electrocardiogram tends to indicate structural heart disease Ashman *et al* (1945) concur with this view but Videla was unable to confirm this statement

Changes of this kind were occasionally reported in the literature and were seen in man

(White Bacq Laubry and Poumailloux Kapff Ashman and Hull) as well as in experimental work (Boer Scherf 1941) An investigation undertaken to establish the frequency of such changes showed that amongst 168 cases with extrasystoles they occurred in fifty seven that is in one third of the cases (Scherf 1944) such alterations of the T waves were seen following ventricular and auricular extrasystoles as well as during auricular fibrillation and A V block with ventricular arrhythmia These cases concerned hospital patients most of them with abnormal hearts The incidence of this phenomenon among healthy individuals with extrasystoles is certainly lower

The mechanism underlying this phenomenon is still obscure and may vary in different cases A few relevant considerations may briefly be mentioned

1 A change of intraventricular conduction may be responsible conduction may temporarily improve owing to the longer post extrasystolic interval available for recovery (Fig 22) or be impaired if this interval is inadequate to compensate for the fatigue caused by the two ventricular contractions in quicker succession

2 The larger diastolic filling during the compensatory pause may produce the changes in the electrocardiogram by altering the size shape and position of the heart and thereby

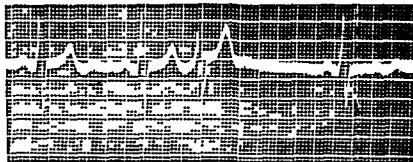


Fig 20—Lead CR-4 The first post extrasystolic sinus beat shows an inverted T wave which in the other sinus beats is upright

its areas of contact with the surrounding tissues This may cause changes in the ventricular electrocardiogram by short circuiting the potentials caused by the depolarization and repolarization of the heart (Lepeschkin) However if this were the underlying mechanism alterations of the QRS complexes would also have to occur in every case

3 A change in the force of contraction of the first post extrasystolic beat also has to be considered It has been shown that in certain circumstances an extra contraction is followed by stronger contractions (Rihl Woodworth) This phenomenon which has been studied in the perfused heart as well as in the heart *in situ* can hardly be responsible for the changes in the electrocardiogram as the length of the post extrasystolic pause was found to be the deciding factor rather than the extra contraction (Scherf 1944)

4 Changes in nutrition of the heart resulting from the extrasystole were considered responsible by some authors (Katz Fernbach) but such changes could hardly become manifest so quickly and be confined to one single beat

5 Changes in contractility and repolarization due to the longer duration of diastole seem so far the most likely possibility (Scherf 1944)

Recognition of this phenomenon may occasionally be of practical importance for instance in the differentiation between auricular and ventricular extrasystoles Fig 21 provides an example Series of seven and fourteen extrasystoles respectively are seen to follow two supra ventricular beats The first of these extrasystoles had a different shape

which was due to its greater prematurity but later in the series changes again were seen (the sixth extrasystole in each group) without any change in rate Aberrant intraventricular conduction is the most probable explanation for the latter observation (p 55) Similar tracings were obtained experimentally during auricular flutter following damage of a bundle branch (Scherf 1929) At first glance the extrasystoles give the impression of being ventricular in origin but closer inspection shows that the T wave of the last sinus beat preceding the groups of extrasystoles was higher than the T waves belonging to the other sinus beats The explanation therefore suggests itself that the higher T wave contained a superimposed P wave and that the extrasystoles were auricular in origin with aberrant intraventricular conduction Other tracings of the same patient however showed that the extrasystoles actually were ventricular in origin and that the difference in the height of the T waves was due to the phenomenon discussed above the higher T waves of the sinus beats were those found during regular sinus rhythm but the first post extrasystolic beats showed considerably lower T waves

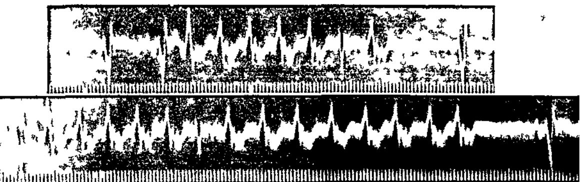


FIG 21 —Lead 3 Multiple ventricular extrasystoles The two strips are continuous The first post extrasystolic sinus beat shows a lower T wave The first and the sixth ventricular extrasystoles of each series are aberrant For further explanation see text

Changes in the post extrasystolic beat may not only affect the T waves but also the QRS complexes though this is rarer In one group of cases an intraventricular block temporarily disappears Thus Fig 22 shows in the top tracing lead 3 from a case with left bundle branch block and in the bottom tracing lead 2 from a case with right bundle branch block In both instances the signs of bundle branch block had disappeared in the post extrasystolic beat In such cases the block has to be considered incomplete in the sense that only a delay of conduction was present the longer interval of recovery available during the post extrasystolic pause was sufficient temporarily to restore normal conduction

In other cases lesser changes in the QRS complex of the post extrasystolic beat are observed for instance decrease in height or increase in depth of one or the other of its waves

(b) Occurrence of heterotopic post-extrasystolic beats

Rarely such post extrasystolic abnormal beats are auricular in origin While abnormal P waves of post extrasystolic beats after *auricular* extrasystoles are common this is rare in those following *ventricular* ones Slight changes in the P waves following two successive ventricular extrasystoles are shown in leads 2 and 3 of Fig 8 Fig 23 obtained from a seventy eight year old patient provides an example of a more pronounced abnormality of this kind The sinus beats show deep Q waves A ventricular extrasystole was followed by a

premature contraction the P wave of which was inverted There is no evidence of a retro grade conduction of the extrasystole to the auricle though this may well have occurred

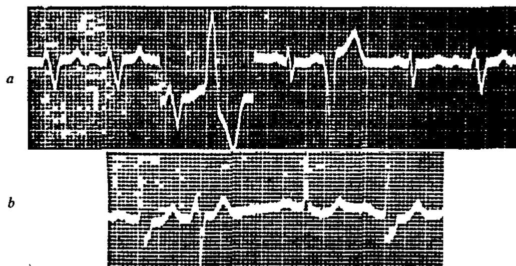


Fig 22 —*a* lead 3 *b* lead 2 In both records the signs of intra ventricular block are absent in the post-extrasystolic beat

More commonly escaped beats which shorten the post extrasystolic pause originate in lower centres In Fig 24 which was obtained from a child with respiratory arrhythmia and ventricular extrasystoles ventricular complexes of normal form and not preceded by P waves were sometimes seen during the post extrasystolic pauses which they terminated Such escaped beats arose presumably in the A V node A highly developed automaticity

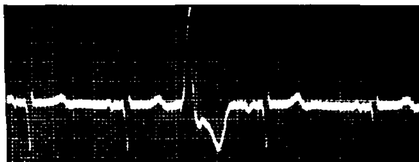


Fig 23 —Lead 3 Abnormal (inverted) P wave in the premature post-extra systolic beat after a ventricular extrasystole

of the lower centres which is responsible for this condition is by no means rare and does not indicate the presence of heart disease

Escaped beats originating in a centre below the bifurcation are shown in Fig 25 taken from a fifty six year old man with moderate hypertension In this case the ventricular extrasystoles were invariably followed by an escaped beat with an abnormal QRS complex In the two instances shown the normal post-extrasystolic beat was due a few hundredths of a second later

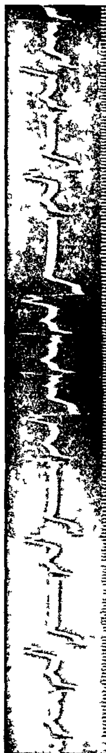


FIG 24 —Escaped beats presumably originating in the A V node following ventricular extrasystoles in a healthy child with respiratory arrhythmia

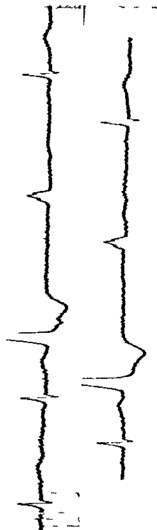


FIG 25 —Lead 2 The two strips are continuous Idioventricular escaped beats following ventricular extrasystoles In the RS T portion of the first extrasystole an inverted P wave is visible indicating retrograde conduction of the impulse to the auricles Time base 0 05 second



FIG 26.—*From an experiment on a dog* Records from above downward indicate signal (stimulation) suspension curve of the right auricle suspension curve of the right ventricle electrocardiogram (lead anus oesophagus corresponding to lead 3) time base 0.02 second Following five ventricular extrasystoles caused by stimulation of the *right* ventricle three *left* ventricular extrasystoles of approximately the same rate occurred

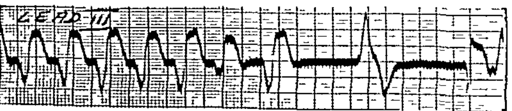


FIG 27.—Lead 3 Following a series of *left* ventricular ectopic beats a *right* ventricular abnormal beat occurred

In experimental work abnormal ventricular and/or auricular beats are sometimes found subsequent to stimulation of the heart Fig 26 was obtained from a dog whose heart was exposed during an experiment Stimulation of the *right* ventricle (the last five of a series of nine ventricular ectopic beats are shown many of which were conducted back to the auricle) was followed by three *left* ventricular extrasystoles The P waves of first five post extrasystolic sinus beats show an abnormal form

Fig 27 illustrates a clinical observation concerning the occurrence of an abnormal ventricular beat following repeated rapid ventricular excitation The record obtained from a sixty eight year old woman two and a half days after an attack of acute infarction of the posterior wall and twenty four hours before death shows auricular fibrillation the

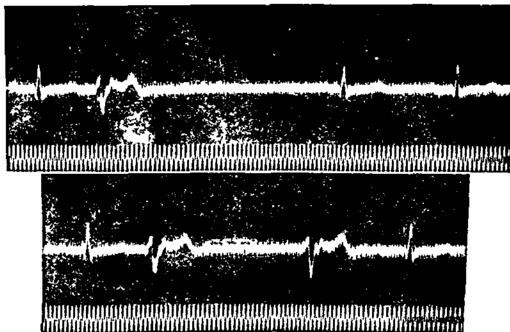


FIG 28 —The two strips are continuous Sino auricular block following ventricular extrasystoles The second extrasystole is followed by an automatic beat

last reproduced complex illustrates the shape of the beats of the dominant rhythm Following an attack of ventricular tachycardia one ventricular complex of an entirely different shape was recorded which indicates that this beat originated in the other ventricle

(c) Occurrence of Abnormal Pauses after Ventricular Extrasystoles

In rare cases of sino auricular block the block appears particularly following a ventricular extrasystole Thus in Fig 28 an interval measuring twice a normal period indicating sino auricular block followed a ventricular extrasystole The second post-extrasystolic pause also due to sino auricular block was shortened by an automatic ventricular beat showing abnormal features The patient had not received digitalis This phenomenon which we observed in two cases of sinus block due to digitalis and coronary sclerosis respectively in one case of coronary sclerosis without digitalis and in one case with

syphilitic aortitis may be a vagal effect by way of reflex each pulse wave producing via the presso receptor nerves a temporary increase in vagal tone sufficient to suppress sino auricular conduction (p 64) (*see* also Fig 17)

In rare cases during rapid sinus rhythm the interval between the last sinus beat before and the first after a ventricular extrasystole equals *three* cycle lengths of the sinus rhythm Fig 29 which illustrates such an observation was obtained from a seventy three year old woman with a recent apical myocardial infarction (note the elevation of the R T junctions and dome shaped convexity of the R T segments) The coupling of the extrasystole plus the post extrasystolic interval equal three cycle lengths of the sinus rhythm Owing to the sinus tachycardia two—instead of the usual one—sinus beats were blocked and failed to yield a ventricular contraction

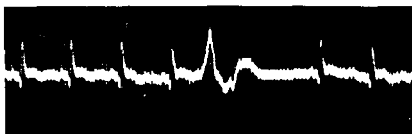


Fig 29 —Lead CF 5 After one ventricular extrasystole the following two sino-auricular impulses are blocked

During digitalis treatment the escape of centres lower in the ventricles is not rare (*see* p 275) In some of these cases the extrasystoles and the escaped beats have identical shapes in the electro-cardiogram which suggests that both originated in the same centre Most of such cases also show auricular fibrillation

It is obvious that at a time when only arterial pulse tracings were available for the analysis of arrhythmias such abnormal post extrasystolic beats appeared to be definite exceptions to the rules of the compensatory pause and that the nature of such exceptions could not be explained

SUMMARY

The nature of the disturbance of rhythm caused by ventricular extrasystoles is discussed and the terminology used in connexion with such arrhythmias defined The electro-cardiographic appearances of ventricular extrasystoles and some relevant features regarding the width of their QRS complexes are discussed It is pointed out that the frequency with which extrasystoles occur varies widely in different cases Examples are given of trigeminal and quadrigeminal rhythm as well as of multiple extrasystoles and of short ventricular paroxysmal tachycardia Changes in the post extrasystolic beats after ventricular extra systoles are discussed under three main headings namely (1) alteration of the features of the first post-extrasystolic sinus beat including the probable mechanism underlying it (2) occurrence of heterotopic post-extrasystolic beats and (3) occurrence of abnormal pauses after ventricular extrasystoles Such changes are discussed in some detail and illustrated by examples

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AURICULAR EXTRASYSTOLES

Extrasystoles originating in an auricle also produce a disturbance of the ventricular rhythm but the factors determining the ventricular arrhythmia and particularly the post extrasystolic pause are more complicated than those prevailing in the case of ventricular extrasystoles

Disturbance of Rhythm

The disturbance of rhythm caused by auricular extrasystoles three different varieties of which are shown is diagrammatically illustrated in Fig 30

The first extrasystole is presumed to have occurred after two normal beats and to have originated rather late in diastole namely 0 54 sec after the preceding beat the normal

period measuring 0 80 sec (Fig 30a) The extrasystole is shown to be conducted both to the ventricles and over a certain distance in a retrograde direction towards the sino auricular node where the next normal stimulus had begun to be formed and had started to spread over the auricles Both excitation waves meet and cancel one another since each meets refractory tissue In such a case stimulus formation in the sino auricular node is not affected by the extrasystole the next normal stimulus being discharged at the normal time

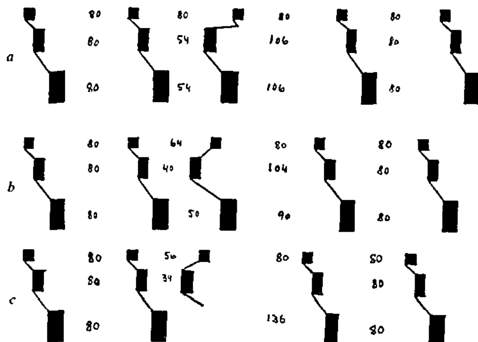


FIG 30—Diagram illustrating the three common disturbances of rhythm caused by an auricular extrasystole which in every graph is the third beat The figures indicate intervals in hundredths of a second *a* An auricular extrasystole occurring comparatively late in diastole is shown conducted to the ventricles and also in a retrograde direction towards the S A node which it fails to reach before the discharge there of the next S A impulse There is no disturbance of the impulse formation in the S A node and the post-extrasystolic interval in the ventricular rhythm is compensatory *b* An auricular extrasystole occurring early in diastole is shown to be conducted to the ventricles and also in a retrograde direction to the S A node which it reaches before the discharge there of the next S A impulse The immature S A impulse is destroyed by the auricular extrasystole with consequent shift of the S-A rhythm the post-extrasystolic interval in the ventricular rhythm is shorter than compensatory *c* Failure of the auricular extrasystole to reach the ventricles blocked auricular extrasystole

The post extrasystolic pause therefore is compensatory (Cushny and Matthews Hering 1901 Wenckebach 1903a)

The second auricular extrasystole shown in the diagram (Fig 30b) is assumed to have occurred earlier in diastole namely 0 40 sec after the preceding sinus beat Again it is shown to be conducted to the ventricles as well as in the reverse direction to the sino auricular node but owing to its greater prematurity it reached the latter before the next normal impulse was completely formed There it discharged the immature stimulus and the next normal impulse had therefore to be built up anew Here again the extrasystole causes a disturbance of the auricular as well as of the ventricular rhythm Unlike the conditions

prevailing with ventricular extrasystoles or with the first variety of auricular extrasystoles discussed above the original rhythm of the heart is not preserved and the post extrasystolic pause when added to the coupling of the extrasystole is shorter than two normal periods that is it is not compensatory

Whether or not an auricular extrasystole is conducted in a retrograde direction to the normal pacemaker and reaches it before the discharge of the next normal impulse depends mainly on its time of occurrence in diastole on the heart rate and on the rate of retrograde and normal conduction If the extrasystole occurs early in diastole and the heart rate is slow the extrasystole is likely to reach the normal pacemaker particularly if the rate of retrograde conduction is high Thus in certain fishes with slow heart rate (40–50 per minute) in which the retrograde conduction is faster than that in the normal direction backward conduction of the extrasystole to the sinus is the rule when the extrasystole occurs within the first fourth to third of the auricular cycle In the tortoise in which the heart rate is also slow (20–30 per minute) such backward conduction is usual In the amphibian heart on the other hand in which retrograde conduction is slow and by comparison with the tortoise the heart rate is higher (about 40) and in reptiles with a higher normal heart rate (lizards snakes) auricular extrasystoles as a rule do not affect the impulse formation in the sinus and the post extrasystolic intervals are therefore compensatory (Skramlik)

In the mammalian heart and in man in the majority of cases auricular extrasystoles disturb impulse formation in the sino auricular node and post extrasystolic intervals that are shorter than compensatory ones are far commoner their existence became known soon after the importance of extrasystoles in the causation of arrhythmias was realized (*see* p 19) Gallavardin measured carefully the post extrasystolic intervals in thirty seven instances of auricular extrasystoles They were found to be compensatory in eleven instances (thirty one per cent) The later in diastole an auricular extrasystole appeared the more frequently was the post extrasystolic pause compensatory

Whereas the length of the *compensatory* post extrasystolic pause whether following a ventricular or auricular extrasystole depends essentially on the rate of the prevailing sinus rhythm and on the time of occurrence of the extrasystole (that is its coupling) a variety of additional factors operate in the case of *non compensatory* post-extrasystolic intervals following auricular extrasystoles which disturb the stimulus formation in the sinus node One important factor is the time required for the auricular extrasystole to be conducted from its focus of origin to the sinus node This time will increase with the distance between the focus of origin of the extrasystole and the sinus node Thus extrasystoles arising near the head of the sinus node will reach this node in a very much shorter time than those originating at a distance say near the A V node Exact measurements showed this assumption to be valid (Lewis Meakins and White) The rate of the reverse conduction of the extrasystole to the sinus node will also be important the more premature the extrasystole the slower the rate of conduction (Wenckebach Drury and Brow Drury and Regnier)

While these considerations are adequate to explain the length of the post extrasystolic interval in many instances this is not the case in all (Cushny 1912) Cushny put forward the suggestion that the breaking of an extraneous stimulus into a centre inhibits the stimulus formation in the centre and his experiments showed that such inhibition is greater the more damaged the heart muscle *Inhibition of stimulus formation by an extra stimulus has been* studied extensively in the automatically beating ventricle (Erlanger and Hirschfelder Hofmann and Holzinger Rothberger and Winterberg Rihl 1913a Miki and Rothberger Scherf and Shookhoff 1925 1926 Eccles and Hoff) but Lewis White and Meakins pointed out that in this respect the sino auricular and atrio ventricular nodes differ from centres producing idioventricular rhythm the S A and A V nodes show inhibition of stimulus formation as a result of an extraneous stimulus only if they are poorly nourished or the heart is in a hypodynamic condition (conditions which can occasionally be assumed to prevail in the human

heart with this kind of arrhythmia) It was also shown that such inhibition of stimulus formation is greater when the extrasystole is early, or when there had been several extra systoles in succession (Hofmann and Holzinger) These results were confirmed by Lewis White and Meakins Miki and Rothberger who devoted a special study to the re examination of the problem emphasized the importance of the inhibition of stimulus formation and also found that the post extrasystolic intervals were lengthened particularly towards the end of an experiment or when the heart had been damaged by asphyxia quinine or muscarine

Whereas all the factors discussed so far tend on the whole to render the post-extra systolic interval longer than the interval between two normal beats this disturbance of rhythm is rendered less conspicuous in the ventricular rhythm as a result of differences in the rate of conduction to the ventricles of the extrasystole and the post-extrasystolic beat Not infrequently auricular extrasystoles are conducted to the ventricles more slowly than the sinus beats and this tends to be the more marked the earlier in diastole the extrasystole occurs The first post extrasystolic sinus beat on the other hand is conducted at the normal rate or faster with the result that the arrhythmia is less marked in the ventricular than in the auricular rhythm Moreover the post extrasystolic interval will be shortened if it is terminated by an escaped beat of idioventricular origin

To sum up the length of the post extrasystolic ventricular interval after auricular extra systoles will depend on

1 the rate of the prevailing sinus rhythm
2 time of occurrence in diastole of the extrasystole
3 sinus arrhythmia itself dependent on nerve tone
4 distance of point of origin of the extrasystole from the S A node
5 rate of retrograde conduction of the extrasystole to the S A node
6 degree of inhibition of stimulus formation in the S A node by the extrasystole dependent on the condition of the heart and perhaps vagal tone
7 rate of conduction of the extrasystole and of the post extrasystolic beat to the ventricles
8 presence or otherwise of an escaped beat terminating the post extrasystolic interval

In view of the number and complexity of these factors it is easily understood that in an individual case it is hardly possible to explain the time relations with any degree of certainty especially as a temporary slowing of the heart also has to be considered as an accidental factor (Lewis 1925) In man the first few cycles following auricular extrasystoles are occasionally shortened (Gallavardin)

If for any reason the conducting system is incapable of conducting the extrasystole to the ventricles the extrasystole is said to be blocked and will fail to yield a ventricular response This condition is illustrated in the third extrasystole of the diagram of Fig 30 (Fig 30c)

The Electrocardiogram of Auricular Extrasystoles

In the electrocardiogram auricular extrasystoles are characterized by premature P waves of normal or more often of abnormal shape in the case of conducted extrasystoles such P waves are followed after a normal or lengthened interval of conduction by a ventricular complex of normal (supra ventricular) or abnormal shape in the case of blocked auricular extrasystoles such P waves are isolated and are not followed by a ventricular complex

With auricular extrasystoles the coupling is measured from the beginning of the P wave of the last normal beat preceding the extrasystole to the beginning of the P wave of the extrasystole

The Shape of the P Waves

*The shape of the P waves of an auric*ular extrasystole depends primarily on its focus of origin but in certain circumstances is also influenced by abnormal spread of the excitation wave within the auricles that is by intra auricular disturbances of conduction The first of these two factors is by far the more important

Auricular extrasystoles originating in the neighbourhood of the head of the sinus node give rise to P waves of the same form as the P waves of the prevailing sinus beats (*see also* section on sinus extrasystoles) Extrasystoles springing from foci situated elsewhere in the auricles yield P waves of different shapes *they may be taller smaller wider slurred* notched inverted or isoelectric in one or the other lead Attempts have been made to deduce the focus of origin of the extra systoles from the shape of the P waves in various leads they are discussed on p 401

Fig 31 was obtained from a dog which had been given 0 1 gm of quinine sulphate intravenously a few minutes before the tracing was taken The ventricular cycles measure 0 64 second (rate 93) Owing to the effect of quinine the P R intervals were lengthened to 0 13 *second and the QRS complexes were* markedly widened By means of a break shock applied to an area close to the head of the sinus node an auricular extrasystole was produced the P wave of which is seen to have a form similar to those of the sinus beats The post extrasystolic *interval was not compensatory The inter*val between the P wave of the extrasystole and that of the post extrasystolic beat measures 0 82 second this is far too long to be explained by the time required for the extrasystole to reach the pace maker in the sinus node even if full *allowance is made for the slowing effect* upon conduction of quinine Inhibition of impulse formation in the sinus node consequent upon the breaking into it of the extra stimulus is the most probable explanation

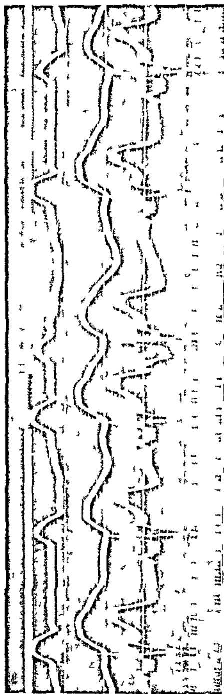


Fig 31 —From an experiment on a dog Tracings from above downward Signal (stimulation) suspension curves of right auricle and right ventricle electrocardiogram (ano oesophageal lead) time base 0 02 second An auricular extrasystole elicited by an induction shock is conducted in a retrograde direction to the sinus node the post extrasystolic interval is not compensatory

In man auricular extrasystoles may occur singly at more or less frequent intervals In

some cases one extrasystole follows each normal sinus beat giving rise to bigeminal heart action or coupled beats moreover auricular extrasystoles may occur in succession in shorter or longer groups Like the ventricular complexes in ventricular extrasystoles the P waves in auricular extrasystoles may maintain the same shape for years A few illustrative cases follow

Fig 32 obtained from a fifty year old man without evidence of heart disease shows auricular extrasystoles after every few sinus beats in lead 3 they occurred after every sinus beat producing bigeminal rhythm due to auricular extrasystoles Except for the extrasystoles the electrocardiogram is normal

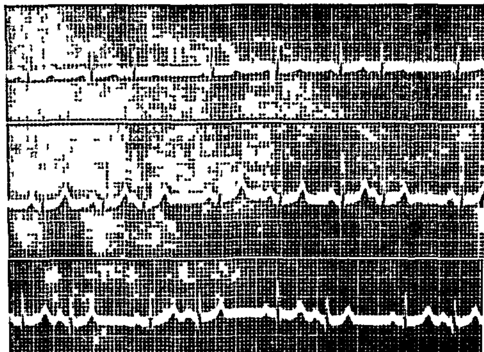


FIG 32 —The three standard leads In leads 1 and 2 one auricular extrasystole after every two or three sinus beats in lead 3 after every sinus beat

Fig 33 provides an example of multiple auricular extrasystoles occurring in succession *three groups each of four are seen to follow a sinus beat This figure also shows another* feature often found in electrocardiograms of auricular extrasystoles namely the (partial or complete) fusion of the P waves of the extrasystole with the T wave of the preceding beat It is obvious that the earlier in diastole the extrasystole occurs the more closely its P wave will approximate the T wave of the preceding beat According to the exact time relations of the two waves and their sizes directions and shapes the P wave of the extrasystole will produce a more or less marked alteration in the shape of the T wave Such changes usually consist of slurring or notching of the T wave or in an increase or decrease in its height such alterations clearly indicating the superimposed P wave If however the changes in the T waves are very slight the recognition of such a wave as containing a P wave may be extremely difficult and in such cases the presence of auricular extrasystoles may easily be missed this holds good especially for lead 1 in which the normal as well as abnormal P

FIG 33 —Multiple auricular extrasystoles The two strips are continuous

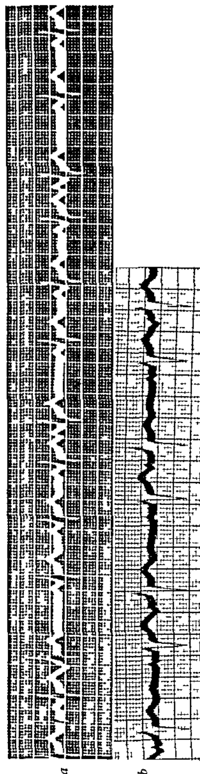


FIG 34 —(*a*) Auricular extrasystoles with varying shape of their P waves (*b*) Lead V 2 Auricular bigeminy with alternation in the shape of the P waves of the extrasystoles

waves often are very small An example of very slight changes in T waves caused by blocked auricular extrasystoles is shown in Fig 40

Auricular extrasystoles occurring singly may show varying shape of P waves (*see* Fig 34a) In auricular bigeminy alternation in the shape of the P waves of the extrasystoles is occasionally observed (Fig 34b) These varieties indicate myocardial disease (*see* section on Prognosis) In cases of myocardial infarction auricular extrasystoles may show typical alterations in their R(S) T segments which need not be present in the sinus beats This is illustrated by Fig 35 The auricular extrasystole recorded in lead 2 shows elevation of the R T junction and pronounced distortion of the R T segment which features are absent in the sinus beats of this lead (For analogous observations in ventricular extrasystoles *see* p 31 and Figs 11 and 12)

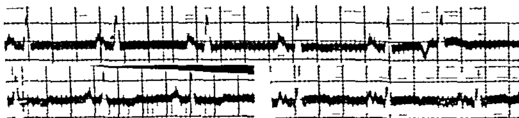


FIG 35 —*Top* lead 2 *bottom* leads 1 and 3 From a patient with a recent myocardial infarction The auricular extrasystole in lead 2 shows in its final deflection the high take off and dome shaped segment characteristic for the lesion whereas these features are absent in the final deflections of the sinus beats in this lead These changes may be due to the Ta wave of the inverted P wave

If several auricular extrasystoles occur in succession the P wave of the first extrasystole may differ in shape from those of the succeeding ones (Fig 44) A similar phenomenon observable with ventricular extrasystoles was described on p 39 its significance is discussed on p 60 *Occasionally the shape of the P wave of the last of a series of auricular* ectopic beats may differ in shape from those of the others (Fig 36a) Fig 36b obtained from a seventeen year old patient with rheumatic mitral valvular disease shows slurred and widened (0 14 second) P waves of the sinus beats features commonly found in this condition The P wave of the auricular extrasystole is not slurred and measures only 0 10 second

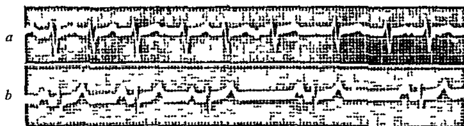


FIG 36 —(*a*) Lead 2 Multiple auricular extrasystoles the P wave of the last of which is different in shape from those of the others (*b*) Lead 1 The gross notching and widening noticeable in the P waves of the sinus beats is absent in the P wave of the auricular extrasystole

The Conduction of Auricular Extrasystoles to and in the Ventricles

Auricular extrasystoles which occur late in diastole are as a rule normally conducted

to the ventricles their P R intervals equal and their ventricular complexes resemble those of sinus beats Auricular extrasystoles of greater prematurity however not infrequently exhibit anomalies in auriculo ventricular and intraventricular conduction three main types of such disturbances may be distinguished

1 Delay of atrio ventricular conduction
2 Failure of atrio ventricular conduction blocked auricular extrasystoles
3 Aberrant intraventricular conduction

1 Delay of Atrio-ventricular Conduction was seen early in his experimental work by Engel mann in 1894 Since delay in the conduction of the premature auricular contraction results in (1) a lesser degree of prematurity of the ventricular contraction and (2) a shortening of the post extrasystolic interval (*see* p 47) the arrhythmia becomes less marked in the ventri cular rhythm than in the auricular one Engelmann referred to this as an automatic self adjustment of the ventricular rhythm If the delay in atrio ventricular conduction of the extrasystole is marked the ventricular contraction may be delayed to such an extent that it occurs almost at the normal time This is often seen in clinical as well as in expreimental work Within certain limits and with certain exceptions (*s below*) the delay in A V conduc tion will be the greater the more premature the extrasystole (Hirschfelder and Eyster Lewis White and Meakins) The condition is illustrated in Fig 42

According to Gallavardin the average P R interval in auricular extrasystoles with in verted P waves in lead 2 was shorter by 0 03 sec than in those with upright P waves in the same lead This suggests that those with inverted P waves originated near the auricular portion of the A V node Some disturbance of the atrio ventricular conduction was found by him in 50 per cent of fifty cases of auricular extrasystoles

2 Failure of Conduction to the Ventricles of an Auricular Extrasystole results in blocked auricular extrasystoles that is premature auricular contractions not followed by a ventri cular contraction This condition also was observed early in experimental work (Engel mann 1894 Hering 1901 Trendelenberg 1909) It was first described in man by Hewlett who offered two possible explanations either the conduction in the A V system is normal and the failure of a ventricular contraction is due to a disturbance of contractility of the muscle or conduction is impaired The second explanation seemed more satisfactory to the author and is now generally accepted Mackenzie attributed the disturbance to the stimulus reaching refractory tissue on its way to the ventricles This early work was soon confirmed experimentally as well as clinically (Rosenthal Robinson and Draper Rihl 1913b) It was found that while the degree of prematurity of the extrasystole is of para mount importance it is by no means the sole decisive factor Thus the observation is not rare that amongst auricular extrasystoles occurring at the same phase of diastole some are normally conducted whereas others are blocked Variations in vagal tone seem of impor tance impaired conduction being found more commonly with a high vagal tone (Robinson and Draper) moreover periodic changes of excitability (Trendelenburg 1903) and the presence or otherwise of a supernormal phase of conduction (p 497) (Ashman) also pay an important part

In lead 1 the P waves of auricular extrasystoles are often very small (*see* Fig 32) or even absent In the case of blocked auricular premature beats the presence of this arrhythmia may thus be missed if only lead 1 is examined and the long interval containing a blocked auricular extrasystole without a visible P wave erroneously attributed to depression of the sinus rhythm or to S A block An instructive example of this kind was reported by Bix (Case 2)

Fig 37a shows numerous auricular extrasystoles characterized by deeply inverted P waves All occurred at about the same phase of diastole but some of them were blocked

FIG 37.—(*a*) Conducted and blocked auricular extrasystoles (*b*) The same but differing from (*a*) by great delay in atrio ventricular conduction



FIG 38.—Long inhibition of impulse formation in the S A node after an auricular extrasystole

whereas others were normally conducted to the ventricles The reason for the differences in conduction in this case is unknown In Fig 37b obtained from another patient three auricular extrasystoles were blocked whereas two others were conducted to the ventricles the P R intervals being lengthened to 0 48 second (The ventricular complex of the last extrasystole is not reproduced)

Blocked auricular extrasystoles may exert a profound influence on stimulus formation in the normal pacemaker as well as on the rate of A V conduction of the following normal beat This suggests that such extrasystoles though not producing a ventricular contraction may in certain cases reach the sino auricular node and be conducted over a certain distance through the A V conducting system before being blocked This assumption is in accordance with experimental findings in the frog (Engelmann) turtle (Ashman) and dog (Scherf and Shookhoff 1925 Lewis and Master)

The first of these two possibilities is illustrated in Fig 38 After two sinus beats occurring at an interval of 1 12 second and showing a lengthened P R interval of 0 28 second a blocked auricular extrasystole occurred The next P wave followed the extrasystole after the long interval of 1 44 second the post extrasystolic interval measuring 2 04 second This very considerable delay in the appearance of the post extrasystolic beat can only be explained by assuming marked inhibition of the stimulus formation in the normal pacemaker which the blocked auricular impulse must have reached

An extreme example of impairment of atrio ventricular conduction caused by blocked auricular extrasystoles is provided by Fig 39 obtained from a sixty four year old patient with coronary sclerosis and angina pectoris The first part of the tracing shows sinus rhythm the P R intervals being lengthened to 0 28 second The fourth and all subsequent sinus beats were each followed by an auricular extrasystole all of them blocked the first one occurring early the others later in diastole With the appearance of auricular extra systoles conduction of the normal sino auricular stimuli to the ventricles ceased and com plete heart block established itself It must be assumed that the blocked auricular extra systoles travelled for a certain distance in the A V system before being blocked and thus further impaired atrio ventricular conduction to such an extent that conduction became entirely interrupted and complete heart block resulted That blocked auricular beats influence the length of the succeeding A V interval was found by several investigators (Engelmann 1894 Ashman Langendorf) Langendorf (Case 1) reported that in this way a subsequent auricular extrasystole may also be blocked

If a blocked auricular extrasystole follows each sinus beat a bradycardia results the underlying mechanism of which may be difficult to elucidate Even if an electrocardiogram is available the diagnosis may not be easy if the extrasystoles occur early in diastole and their P waves superimposed on the T waves of the preceding beat produce only slight alterations of the shape of the latter (*see* p 57) Thus in Fig 40 only a very slight slurring of the T waves indicates that the third fourth and fifth beats are each followed by a blocked auricular extrasystole In such cases other leads particularly certain chest (V 1) or oeso phageal leads often are helpful

Large U waves occasionally may be mistaken for blocked auricular extrasystoles Fig 41 shows both kinds of waves which differed conspicuously from one another by their different shape and direction

3 **Aberrant Intraventricular Conduction** As auricular extrasystoles are due to supra ventricular impulses which are conducted to the ventricles through the normal pathways it is to be expected that the ventricular complexes resemble those of the sinus beats in a given case While this holds good in many instances (*see* Figs 32 41) anomalous ventricular complexes associated with auricular extrasystoles indicating abnormal spread of the im pulse through the ventricles were found soon after the electrocardiographic method had become available for the study of the spread of the excitation wave (Lewis 1910 and 1912

and Rosenthal using one of Lewis s cases) This phenomenon was called aberration by Lewis who defined it as abnormal distribution of the supraventricular impulse in the ventricle (1925 p 517)

Such abnormalities of the ventricular complexes may be very slight consisting only of an increase or decrease in the height or depth of one or the other of the waves or the appearance or disappearance of one of the small (particularly Q) waves In other instances however the ventricular portions may be widened slurred or notched to such an extent that

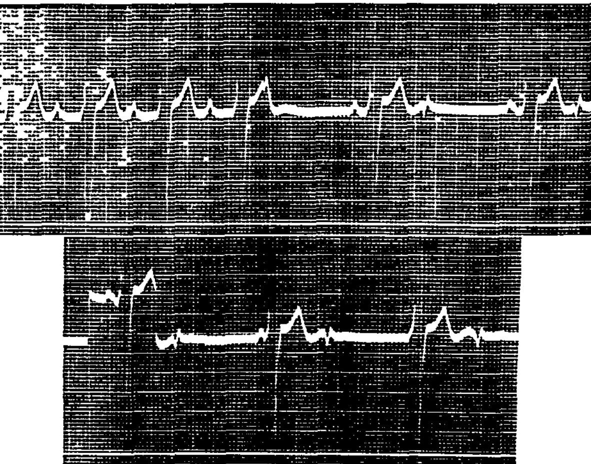


FIG 39 —Lead 3 The two strips are continuous The beginning of the record shows sinus rhythm with P R intervals lengthened to 0 28 second Subsequently with the occurrence of blocked auricular extrasystoles this first degree of A V block changes into a complete one

they closely resemble ventricular extrasystoles and may easily be confused with them unless due attention is paid to the fact that they are preceded by P waves at intervals usually found with A V conduction Confusion with ventricular extrasystoles is particularly apt to occur if the degree of aberration remains the same from beat to beat (which is much less common than a varying degree) or if the premature P wave is buried in the final deflection of the preceding beat Even regular alternation between two forms of aberrant QRS complexes has been described (Stenström 1923 1924)



Fig 40 —Blocked auricular extrasystoles causing only very slight changes in the T waves of the preceding beat



Fig 41 —Lead I Auricular xtrasystoles and pronounced U waves

Generally speaking aberration tends to occur and to be more marked the earlier in diastole the extrasystole occurred It will be seen however that other factors also are of importance

Thus Fig 42 obtained from a twenty one year old woman shows auricular extrasystoles in each lead In lead 1 on two occasions the P waves of the extrasystoles were fused with the T waves of the preceding beats which they rendered slightly higher and more peaked the second auricular extrasystole occurred later in diastole and its P wave is very low In leads 2 and 3 the P waves of the extrasystoles were deeply inverted Aberration of some degree is seen with each extrasystole but even if extrasystoles occurred in the same phase of diastole the degree of aberration and even the direction of the main deflection of the



FIG 42—The three standard leads Auricular extrasystoles with aberrant intra ventricular conduction The tracings illustrate that this is not solely dependent on the degree of prematurity of the extrasystole For further explanation see text

ventricular complexes may vary (cf the first and last extrasystole in lead 1 and the second and third in lead 2) Fig 43 reproducing two tracings obtained from the same patient shows auricular extrasystoles after each sinus beat some of which were normally conducted others aberrantly and others again were blocked Here again the degree of prematurity or length of coupling of the extrasystole to the preceding beat obviously could not have been the sole deciding factors

Experimental and clinical observations have shown that in such cases some other disturbance of conduction often of a minor degree or even latent is present

Experimentally aberration was found to occur after previous damage of the A V system (Stenstrom) After slight mechanical damage to the right bundle branch with subsequent recovery of normal conduction auricular extrasystoles were followed by ventricular complexes of the bundle branch block type Moreover if at this moment of the

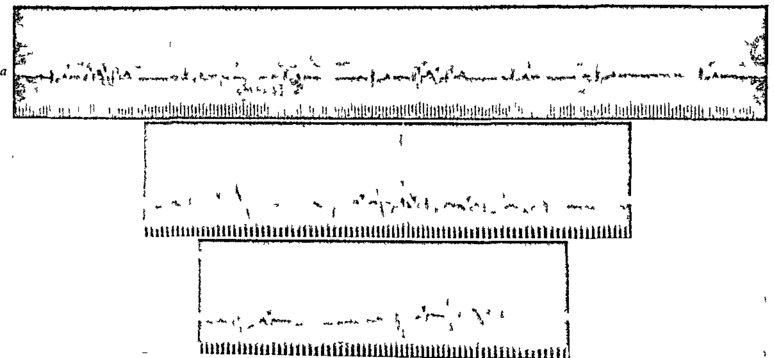


Fig 43 —Auricular extrasystoles some with normal some with aberrant intraventricular conduction and some of them blocked
The middle and bottom strips are continuous

experiment the conducting system was fatigued by a series of ventricular extrasystoles produced in rapid succession the following sinus beats temporarily showed the features of right bundle branch block (Scherf, 1927) Lewis (1925) found that beats of this kind could be obtained more easily in the cat when the heart presented slight changes of conduction for instance during asphyxia

Fig 43 illustrates another observation which is by no means rare namely that the first of a series of auricular extrasystoles shows a particularly delayed conduction and marked degree of intraventricular aberration Thus in Fig 43a one blocked auricular extrasystole followed each normal beat except for two occasions when two conducted extrasystoles occurred in succession The first extrasystole of each of these two groups showed a delayed A V conduction of 0 24 second followed the preceding beat after 0 44 second and their ventricular complexes showed marked aberration The second extrasystole of each group which was conducted at a normal rate to the ventricles followed the preceding beat (the first extrasystole of the group) at an interval of only 0 36 second and their ventricular complexes showed less aberration Similar conditions are shown in Fig 43b in the second half of which an auricular extrasystole with delayed A V conduction and a coupling of 0 42 second was aberrantly conducted whereas the succeeding one following after only 0 34 second with a normal P R interval had an almost normal ventricular complex (*see* also Figs 57a and 58 in the section on A V extrasystoles)

These observations which tend to prove that the degree of prematurity cannot be the sole decisive factor to account for the presence or degree of aberrant intraventricular conduction at first sight are surprising in another respect One would expect that with a succession of extrasystoles the degree of disturbance of conduction both atrio ventricular and intraventricular would gradually increase whereas the records clearly show the first extrasystole to be most affected in this respect Moreover it is by no means rare that also with longer series of auricular extrasystoles the first one displays particularly marked delay in A V conduction and degree of intraventricular aberration Similar observations were made in cases of periodically dropped beats (Scherf 1929) Another observation relevant in this connexion is that in a series of ventricular extrasystoles the first one may be different from the others in the electrocardiogram (*see* Fig 21) or more rarely in a series of auricular extrasystoles the shape of the P wave of the first one may differ from that of all subsequent ones (Fig 44 lead 2)

Consideration of the refractory phase seems to afford the explanation It has been established that the refractory period shortens as a result of increased heart rate (Trendelenburg 1903 Mines Lewis Drury and Bulger) and of fatigue (Adrian) and the refractory period of a premature contraction was found to be shorter than that of a beat occurring after a longer interval (Trendelenburg 1903 Junkmann) (*See* also section on Dynamics and Refractory Period) The assumption seems justified therefore that beats occurring after long intervals (for instance the sixth beat of Fig 43a which was a post extrasystolic beat after a long post extrasystolic interval) have a long refractory period so that an extrasystole following on such a beat will find the tissue only partially recovered the disturbed conduction resulting from partial refractoriness (Lewis 1925) will account for delayed A V as well as for aberrant intraventricular conduction The extrasystole itself having a shorter refractory period will not affect conduction of a subsequent extrasystole to the same extent hence disturbances of conduction are less marked in the remaining extrasystoles of a group as compared with the first one (Scherf 1929)

Other factors of importance in this connexion are toxic damage of the heart for example by quinidine which tends to make aberration more pronounced (Berliner and Lewithin) and vagal tone Since stimulation of the vagus is known materially to shorten the refractory period of the dog s auricle and thereby indirectly to improve conduction of impulses falling within the period of recovery from a preceding beat variations of vagal

tone may well account for the different behaviour of auricular extrasystoles occurring in man under otherwise seemingly identical conditions Since there is no evidence of a direct action of the vagus on the mammalian ventricle the intraventricular conduction is not influenced directly by a change in vagal tone

Reports about the incidence of aberrant conduction of auricular extrasystoles give varying figures White and Stevens found it in eleven out of twenty three cases Palmer and

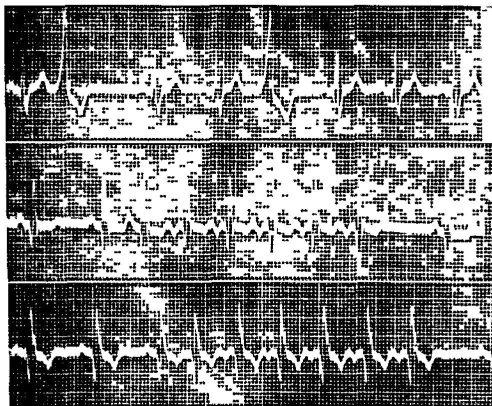


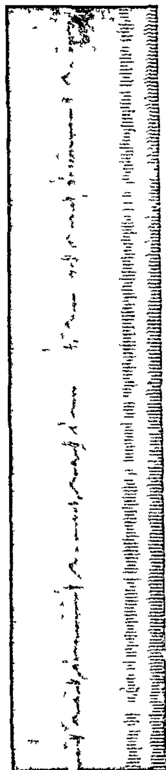
FIG 44—The three standard leads The record indicates right bundle branch block In leads 2 and 3 multiple auricular extrasystoles in lead 2 the P waves of the first beat of the series are upright whereas those of the remaining ectopi beats are inverted The premature beats in lead 1 may b ventri ular extrasystoles but auricular origin with aberrant intra ventricular conduction cannot be excluded

White saw it 107 times in a series of 387 cases in a more recent series of fifty cases it occurred in twenty three (Gallavardin) It seems certain that this phenomenon is common and it was claimed that more auricular extrasystoles were followed by abnormal ventricular complexes than by normal ones (Berliner and Lewithin)

If successive auricular extrasystoles follow one another at irregular intervals differ entiation from auricular fibrillation can only be made electrocardiographically Fig 36a illustrates this condition showing moreover the extrasystoles to have varying P R intervals

Occurrence of Heterotopic Beats following an Auricular Extrasystole

Just as in the case of ventricular extrasystoles the post extrasystolic interval following


Fig 45 —Blocked auricular extrasystoles followed by an escaped beat

auricular extrasystoles may be terminated by an escaped beat originating in a centre other than the normal pacemaker Escape of a lower centre is particularly apt to occur after blocked auricular extrasystoles as here the post extrasystolic interval tends to be particularly long Fig 45 shows a blocked auricular extrasystole occurring after each group of two normal beats the post extrasystolic interval being invariably terminated by an escaped beat originating in the A V node (The normal P wave of the sinus beat due to occur shortly after the escaped beat is visible between the QRS complex and T wave of the escaped beats)

In other instances the post extrasystolic interval is terminated by supra ventricular beats showing abnormal P waves Thus Fig 46a taken from a patient with rheumatic mitral valvular disease shows widened and notched P waves The two beats following an auricular extrasystole exhibit different and grossly abnormal P waves The post extrasystolic interval is not compensatory Such abnormal P waves of beats following an auricular extrasystole usually have the same shape as that of the extrasystole (observed also in oesophageal leads Enselberg) but exceptions occur In Fig 46b the auricular extrasystole had a distinctly positive P wave whereas the P waves of the three following beats were very low and gradually increased in height Intra auricular disturbances of conduction may also play a part The same phenomenon could frequently be observed in experiments on dogs (Rothberger and Scherf)

Usually this phenomenon is transitory and only found in the first few post extrasystolic beats The post extrasystolic interval tends to be equal to or slightly shorter than that found without alterations of the P waves of the post extrasystolic beats

In his first description of this phenomenon Lewis (1912) pointed out that the discharge of the abnormal extrasystolic impulse may precipitate formation at the same site of the next impulse to be discharged at the time it is due This view is supported by the experimental observation that following rhythmical stimulation of the auricle the first impulse after the end of stimulation may arise in the stimulated area and not the normal pacemaker (Skramlik Rachmilewitz and Scherf Bloch) Abnormal centres other than the centre of origin of the extrasystole also may temporarily give rise to impulses after the post extrasystolic interval

Post extrasystolic beats following auricular extrasystoles whether blocked or conducted may show the same kind of alterations of T waves as were described regarding those following ventricular extrasystoles (p 37)

Differentiation between Blocked Auricular Extrasystoles and 2 1 A V Block

It is well known that in 2 1 A V block those P P intervals which contain a conducted beat often are shorter than those without it the P wave following a ventricular complex occurring slightly prematurely as compared with the subsequent P wave Moreover the

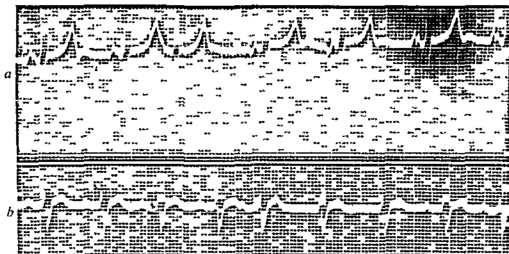


FIG 46—Both tracings lead 1 from different patients Changes in the shape of the P waves of the first few post extrasystolic sinus beats after an auricular extrasystole For further explanation see text

premature P waves in 2 1 A V block may differ in shape from the others (Scherf 1945) This sequence a conducted beat followed by an isolated premature P wave of different shape obviously would fit both with a diagnosis of blocked auricular extrasystoles and that of 2 1 A V block and special measures may be necessary to arrive at a differential diagnosis the clinical importance of which is considerable Fig 47 obtained from an eighteen year old patient with rheumatic fever provides an example It shows conducted beats the P R intervals being lengthened to 0 24 second followed by slightly premature P waves which



FIG 47—Lead 2 2 1 A V block simulating blocked auricular extrasystoles

were slurred and differed in their appearance from the P waves preceding the ventricular complexes Blocked auricular extrasystoles could not be ruled out by the reproduced record alone Even slight exercise however will temporarily abolish extrasystoles while a 2 1 block will temporarily be converted into periodically dropped beats or into a block of higher

degree (say 3 1) and the differential diagnosis will be made possible in this way Other tracings of the same patient revealed that actually 2 1 A V block was present in Fig 47

[The mechanism underlying the changes in the time relations and shape of P waves in 2 1 block is not fully understood periodical changes in vagal tone are the most likely explanation each pulse wave following a ventricular contraction producing a temporary increase in vagal tone via the pressor receptor nerves (Erlanger and Blackman Ashman and Gouaux Scherf 1945)]

Combination of auricular and ventricular extrasystoles in the same patient

This combination of ectopic beats is occasionally observed but is not very common Figs 48 and 49 provide examples

Fig 48 obtained from a sixty six year old man with hypertension shows also the un usual feature that a ventricular extrasystole mostly occurred immediately after an auricular one (top record) but this was not invariably the case as illustrated in the bottom record

Fig 49 recorded in a twenty three year old man with attacks of paroxysmal tachy cardia while on a preventive maintenance dose of quinidine shows in its middle portion auricular bigeminy The third beat is an auricular extrasystole with gross aberration of intra ventricular conduction Its P wave is recognizable as a notch in the ascending limb of the preceding T wave (R P = 0 4 second P R = 0 26 second as compared with the R P of 0 48 and P R of 0 16 second of the extrasystoles of the bigemini with normal intra ventricular conduction) The penultimate beat is a ventricular extrasystole The disturbances in intra ventricular conduction of the sinus beats are attributable to quinidine

Fig 44 may be another instance showing ventricular extrasystoles in lead I and auricular ones in leads 2 and 3 though the ectopic beats in lead 1 may be auricular in origin with aberrant intraventricular conduction Such possibility has to be considered particularly as the P waves of auricular extrasystoles are often very small or absent in lead I

According to Huppert and Berliner the occurrence of both auricular and ventricular extrasystoles is strongly suggestive of cardiac disease In one series of the e authors all the twenty five patients in whom this combination was encountered were suffering from cardiac disease In another series of twenty one cases in whom sinus tachycardia (rate 100 and over) was present in addition only two patients were free from cardiac involvement

SUMMARY

Three main varieties of disturbances of rhythm caused by auricular extrasystoles are distinguished and illustrated diagrammatically auricular premature beats without and with conduction of the ectopic impulse to the S A node and therefore without and with shifting of the dominant rhythm and blocked auricular extrasystoles The numerous and complex factors determining the length of the post extrasystolic interval in the ventricular rhythm are discussed and analysed

The electrocardiogram of auricular extrasystoles is described in detail under three main headings

A Shape of the P waves including some special features such as bigeminal rhythm due to one auricular extrasystole following each sino auricular beat diagnostic difficulties arising out of the superposition of small P waves on the T of the preceding beat and pecu liarities of the P waves in auricular extrasystoles occurring in succession

B Conduction of auricular extrasystoles to and in the ventricles Three main aspects of this are discussed

(1) Delay of A V conduction It is pointed out that while the degree of prematurity is the most important factor in determining the length of the A V conduction time of an

FIG 48 —Lead aVR The two strips are continuous Auricular and ventricular extrasystoles For further explanation see text

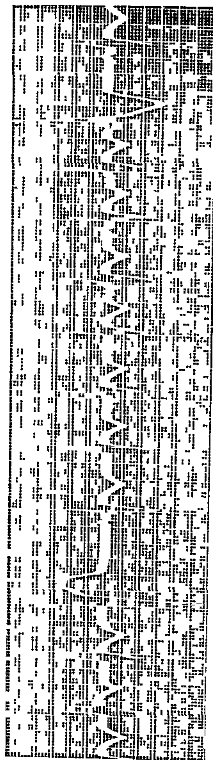


FIG 49 —Lead V 2 Auricular and ventricular extrasystoles For further explanation see text

auricular extrasystole this is not the only one and others discussed under (2) have to be considered

(2) Failure of conduction to the ventricles of an auricular extrasystole blocked auricular extrasystoles While the degree of prematurity of the ectopic beat is the most important factor determining whether or not the impulse reaches the ventricles variations in vagal tone changes in excitability of the ventricles and the presence or otherwise of a supernormal phase of conductivity also play an important role Blocked auricular extrasystoles may exert a profound influence on impulse formation in the S A node and on the rate of A V conduction this is illustrated by clinical examples

(3) Aberration of intra ventricular conduction This tends to occur, and to be more marked the earlier in diastole the extrasystole occurs but other factors are also of importance these are briefly discussed The observation that in a series of successive auricular extrasystoles the first may show aberration while in the remaining ectopic beats of the series this is absent is explained by the length of the refractory period preceding the first and the subsequent beats respectively of such series Other factors are toxic damage to the heart and variations in vagal tone in the auricles

C The occurrence of heterotopic beats occurring after an auricular extrasystole and terminating the post extrasystolic interval Several varieties of such beats are discussed and their electrocardiographic appearance is illustrated by examples

The difficulties which may arise in distinguishing between periodically occurring blocked auricular extrasystoles and 2 1 A V block are briefly discussed

Instances of a combination of auricular and ventricular extrasystoles in the same patient are described

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ATRIO VENTRICULAR EXTRASYSTOLES

Introductory Remarks

Extrasystoles originating in the atrio ventricular (A V) node were first described by Pan and by Volhard both in 1904 before the discovery of the A V node but misinterpreted as ventricular extrasystoles with retrograde conduction to the auricles In the same year Mackenzie published the tracing of an A V extrasystole which however is not described as such In 1906 extrasystoles originating in the A V node in monkeys were described by Hering and considered to have been due to increased resistance to the emptying of the left ventricle The first clinical examples of this arrhythmia were those of Hering and Rihl (1906) Ritchie (1907) and Mackenzie (1908) Subsequently cases were described by Lewis Wenckebach and Winterberg and others

The diagnosis of A V extrasystoles and our conception about their site of origin within the A V node as well as their mode of conduction are based on our knowledge of A V nodal rhythm

The origin of the impulse in the A V node results in the spread of the excitation wave through auricles and ventricles in such a way that their contraction occurs more nearly *simultaneously than with any other site of origin of impulse formation* Moreover while the direction of the spread of the excitation wave through the ventricles is the same as that of beats of supraventricular origin in the auricles it is the reverse By studying the curves of the momentary electrical axes (vectors) in A V nodal rhythm Ruskin and Decherd found them to pass upwards backwards and to the left as compared with a downward and forward course to the left in sinus rhythm

Upper middle and lower A V rhythm and A V extrasystoles

A V rhythm and A V extrasystoles were further subdivided according to whether activation of the auricles precedes coincides with or follows that of the ventricles In the electrocardiogram these three groups are characterized by the position of the P waves in relation to the QRS complexes the P waves preceding coinciding with or following the QRS complexes respectively

For a considerable time in the past the position of the P waves in relation to the QRS complexes was taken to indicate the site of origin within the A V node of such beats This view was based on the results of the early experiments of Ganter and Zahn and of Zahn regarding the effects upon the sequence of auricular and ventricular contraction of warming separate portions of the A V node also on Meek and Eyster s experiments on the site of primary negativity in different kinds of A V rhythm This interpretation was accepted by Clerc and Pezzi Wenckebach and Winterberg (pp 143 199) and others For different reasons Lewis though he considered the exact location of events in a small structure buried under septal muscle precarious believed it to be correct

This conception some suggested modifications of which will be discussed below is diagrammatically illustrated in Fig 50 In Fig 50a origin of the A V beat in the upper (auricular) portion of the A V node is assumed As the centre of impulse formation lies nearer to the auricles than to the ventricles and the A V node is known to delay the propagation of the impulse the auricles are activated before the ventricles and in the electrocardiogram a P wave precedes the QRS complex with a more or less shortened P R interval With the impulse originating in the middle portion of the A V node (Fig 50b) the conduction times from the centre of origin of the impulse to the auricles and ventricles respectively are approximately equal Both chambers are therefore activated simultaneously with the result that the P wave will be inscribed at the same time as the QRS complex and

thus buried in it If the impulse originates in the ventricular portion of the A V node as shown in Fig 50c the auricles will be activated later than the ventricles and the electro cardiogram will show a negative P R (or an R P) interval a P wave following the QRS complex

The Electrocardiogram

General Features

These considerations about the direction of spread of the excitation wave and the sequence of auricular and ventricular activation explain the electrocardiographic features in the different varieties of A V extrasystoles

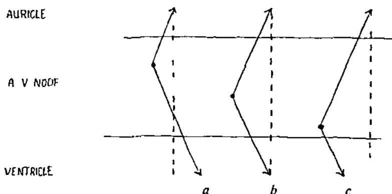


FIG 50 —Diagram illustrating the three varieties of A V rhythm and or A V extrasystoles

In the standard limb leads they are characterized by premature ventricular complexes of supraventricular shape

(a) which are preceded or followed by P waves which are low positive or iso electric in lead 1 and sharply inverted and often peaked in leads 2 and 3

or

(b) in relation to which separate P waves are absent

In those forms of (a) in which a P wave precedes the ventricular complex the P R intervals are often abnormally short. In the variety (b) the P wave being inscribed simul taneously with and buried in the QRS complex often produces some alteration in the shape of the latter

In the augmented unipolar right arm lead aVR the P waves of A V beats are upright (whereas those of sinus beats are inverted in this lead) in the unipolar left leg lead aVF A V beats show inverted P waves (*see* Fig 58)

Fig 51 obtained from a seventy five year old woman with coronary sclerosis repro duces A V extrasystoles with preceding activation of the auricles One extrasystole is seen in lead 1 showing a low upright P wave Two extrasystoles are seen in leads 2 and CR-4 respectively and one in lead 3 all showing deeply inverted P waves and P R intervals shor tened to 0 08 second as compared with the 0 13 second of the sino auricular beats The presumed site of origin of the extrasystoles is the auricular portion of the A V node The post extrasystolic intervals are compensatory which indicates that the retrograde activation of the auricles did not interfere with the normal impulse formation in the S A node this is attributable mainly to the prevailing sinus tachycardia of 106 per minute

Fig 52 provides an example of an A V extrasystole with simultaneous activation of auricles and ventricles After three sinus beats a premature ventricular complex having almost the same shape as those of the sinus beats was recorded in connexion with which no P wave is visible The post extrasystolic interval was compensatory Since in relation to such premature contractions P waves were also absent in all other leads simultaneous activation of auricles and ventricles has to be assumed Close inspection of the QRS complex of the extrasystole shows that the R wave is smaller and the S wave deeper than the corresponding waves of the sinus beats These differences have to be ascribed to the presence of an inverted P wave buried in the QRS complex In order to be certain that auricles

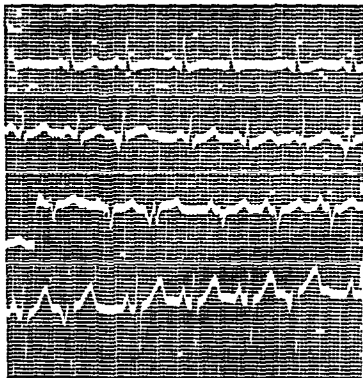


FIG 51 —The standard leads and lead CR-4 A V extrasystoles with preceding activation of the auricles presumably originating in the upper portion of the A V node Their P waves are shallow and upright in lead 1 and sharply inverted in the remaining leads The P R interval of the extrasystoles is shortened

and ventricles contracted simultaneously a record of the venous pulse is necessary in which an A V extrasystole manifests itself by a premature high wave consisting of the auricular *a* wave superimposed on the ventricular *c* wave In such cases the extrasystole is believed to originate in the middle portion of the A V node

Figs 53 and 54 provide examples of A V extrasystoles with preceding activation of the ventricles presumed to originate in the ventricular portion of the A V node

Fig 53 obtained from a forty eight year old healthy woman shows a premature ventricular complex of supraventricular shape after which a shallow inverted P wave is visible between the QRS and T waves The post extrasystolic interval was not compensatory

In Fig 54 two A V extrasystoles in each of the three leads are seen the P waves following the QRS complexes being very shallow in lead 1 and sharply inverted in leads 2 and 3 The post-extrasystolic intervals were not compensatory and the intervals between the inverted P waves of the extrasystoles and the P waves of the next S A beats were slightly longer than those between two sinus beats These time relations are reminiscent of those in ventricular extrasystoles in complete A V block and are most likely due to the same mechanism destruction of the immature impulse in the centre of the dominant rhythm by the extra systole with slight inhibition of impulse formation

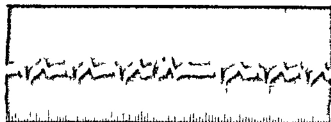


Fig 5. —Lead 2 A V extrasystole with simultaneous activation of auricles and ventricles presumably originating in the middle portion of the A V node The P wave of the extrasystole is buried in its QRS complex

In cases with preceding activation of the ventricles the P wave of the extrasystole may occasionally show every intermediate form between being sharply inverted in leads 2 and 3 as described and that of normal sinus beats This is due to interference between the retro grade activation of the auricles from the extrasystolic focus and the orthograde one from the sino auricular node This phenomenon will only be observed in extrasystoles occurring very late in diastole at a time when the next normal impulse is due

The length of the post extrasystolic intervals after A V extrasystoles depends on the same factors as that following auricular ones and may be compensatory or shorter than compensatory No data are available as to which of these two varieties is commoner

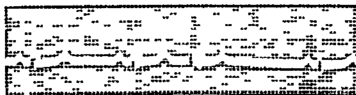


Fig 53 —Lead 3 A V extrasystole with preceding activation of the ventricles presumably originating in the lower portion of the A V node Its inverted P wave is visible between the QRS complex and T wave

Coronary sinus rhythm and coronary sinus extrasystoles

Attempts have been made (Zahn Scherf and Harris Michaelides and Costeas) to separate from a rhythm originating in the upper portion of the A V node and showing inverted P waves in leads 2 and 3 with a *shortened* P R interval another form in which the P waves show the same shape but the P R interval is *normal* There are good reasons for the assumption that such beats originate in an area close to the orifice of the coronary sinus vein and this kind of rhythm has therefore been termed coronary sinus rhythm There is experimental evidence that this area possesses a high degree of automaticity (Zahn Scherf 1944) and records obtained in the dog of beats produced by stimulating this area

show the same features as tracings which are relatively common in man (In our opinion this type of A V rhythm is commoner than all the other types and has frequently been mis interpreted in clinical electrocardiography) Extrasystoles showing the form of P waves in the different leads as described above and associated with a normal P R interval should therefore be called coronary sinus extrasystoles

It is however not possible to separate coronary sinus extrasystoles from upper nodal A V ones with any degree of certainty because the length of the P R interval of such beats on which the distinction has to be based is profoundly affected by disturbances of conduction This is discussed below

The term coronary sinus rhythm was also applied in our opinion erroneously to a type of tracing showing normal P waves with shortened P R intervals (Katz) We believe that such tracings do not indicate an ectopic site of impulse formation but sinus rhythm

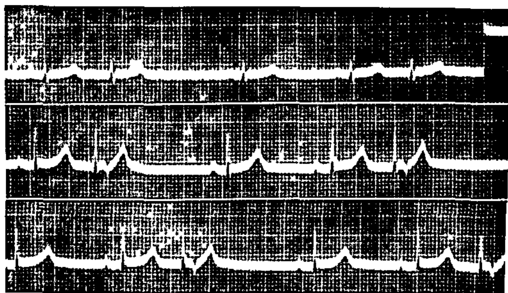


FIG 54 —The standard leads A V extrasystoles with preceding activation of the ventricles presumably originating in the lower portion of the A V node

which in certain conditions (left ventricular strain in certain types of hypertension vitamin B_1 deficiency) may be associated with a shortened P R interval (Scherf *1941*) The use of the term coronary sinus rhythm for this kind of record does not appear to be justified and since it also tends to confuse the issue should be discouraged

The effect of disturbances of conduction upon the electrocardiogram of A V extrasystoles

While a more detailed review of the conditions influencing the electrocardiogram in cases of A V rhythm is outside the scope of this book it may be said that some objections have been raised as to the validity of the scheme on which our discussion of the various types of A V rhythm and A V extrasystoles has been based Such objections are mainly founded on the following observations The position of the P waves in relation to the QRS complexes is determined not only by the site of impulse formation within the A V node but also by the rate of conduction of the impulse into the auricles and ventricles respectively slight changes of which may produce marked alterations in the P R or R P intervals in A V rhythm Moreover intra auricular disturbances of conduction may profoundly affect the

shape of the P waves in A V rhythm (Scherf and Shookhoff 1926) and sinus rhythm (Rothberger and Scherf)

A few examples Temporary disturbances of conduction in the bundle of His may produce a temporary lengthening of the P R intervals though the centre of impulse formation remains unchanged in the lower portions of the A V node (Scherf and Shookhoff 1925) inverted P waves with normal P R intervals do not necessarily exclude an origin of the extrasystole in lower parts of the A V node as they may be the result of delay in conduction (Scherf 1931 *see also* diagrammatic illustration of Fig 55 and section on the influence of extrasystoles on A V rhythm p 102) upper nodal (and coronary sinus) rhythm may be associated with P R intervals exceeding 0 12 second the length of this interval being sometimes but not invariably related to the length of the P R interval of the sinus beats in the same patient (Scherf and Harris) also in experimental coronary sinus rhythm in the dog P R intervals exceeding 0 12 second were occasionally observed (Scherf 1944)

This view has been accepted by others For instance Langendorf Simon and Katz believe that sharply inverted P waves in leads 2 and 3 with P R intervals exceeding 0 12 second indicate A V rhythm with A V block rather than sinus rhythm with intra auricular disturbances of conduction In our opinion this is usually coronary sinus rhythm

A further degree of disturbances of conduction is the complete blocking of the impulse of an A V extrasystole in one or other direction Instances of blocked conduction to the

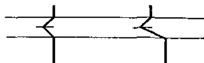


Fig 55 —Diagram illustrating the effect in A V rhythm upon the position of the P wave in relation to the QRS T complex of disturbances of conduction in the A V system

ventricles were published by Dack and Mond and by Holzmann (p 465) In the first mentioned case two coupled extrasystoles occurred at times The venous pulse tracing taken in addition to the electrocardiogram proved both beats to have been of A V origin though only one of them produced an inverted P wave whereas the other showed simultaneous activation of auricles and ventricles P waves were visible only when owing to block in the ventricles no QRS complex was inscribed—an instructive example of the importance of disturbances of conduction in determining the features of A V extrasystoles in the electrocardiogram

Langendorf and Mehlman described a case in which A V extrasystoles with blocked conduction to auricles as well as to ventricles could be diagnosed with a great degree of probability Obviously with conduction blocked in both directions such extrasystoles could not give rise to either auricular or ventricular waves in the electrocardiogram but their presence could be deduced by the disturbance of the sinus rhythm which they caused This consisted in either a sudden lengthening of the P R interval of the following sinus beat or a dropped beat without any preceding increase of the P R interval A similar observation concerning interpolated A V extrasystoles was described by Bix (Case 1)

Revised classification of the various types of A V rhythm and A V extrasystoles

In view of such observations it has been thought that it is no longer permissible to distinguish an upper middle and lower nodal rhythm according to the position of the P waves in relation to the QRS complexes Instead it has been proposed that this classification should be replaced by distinguishing A V rhythm (and A V extrasystoles) (a) with preceding

auricular (b) with simultaneous auricular and ventricular and (c) with preceding ventricular activation (Holzmann p 460) While we do not intend to pronounce any final judgment as to the extent to which it is possible to deduce from electrocardiograms the site of origin within the A V node of impulses in A V rhythm and A V extrasystoles in our opinion such a determination is possible with a fair degree of probability at least as far as a distinction between impulse formation in the upper (including coronary sinus area) and lower portions of the A V node is concerned This view is also supported by the differences in anatomical structure of the various portions of the A V node (Kung) and by the absence in a large proportion of cases of any signs of disturbances of conduction A distinction between coronary sinus and upper nodal rhythm is not possible with any degree of certainty as already referred to

A V extrasystoles with upright P waves in leads 2 and 3

In the dog upright P waves in A V rhythm can be found in the ano oesophageal lead (closely corresponding to lead 3) particularly in instances of altered intra auricular conduction due to certain poisons (Scherf and Shookhoff 1926)

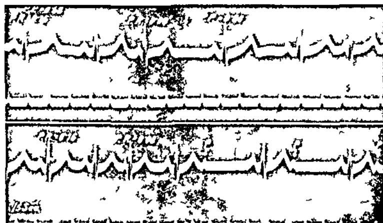


Fig 56 —Top tracing lead I bottom tracing lead 2 A V extrasystoles with upright P waves some with blocked ventricular conduction From McGuire and Rosenberger *Z Kreisl Forsch*

Electrocardiograms in man showing A V rhythm with upright P waves in leads 2 and 3 *preceding QRS complexes of normal supraventricular shape with shortened* P R intervals are rare but the few clinical records of this kind which have been published can best be explained by the assumption of an A V origin of such rhythms (Holzmann and Scherf) The most convincing case in which such beats occurred as extrasystoles is the one reported by McGuire and Rosenberger from whose paper Fig 56 is taken In the upper tracing two normal sinus beats with a P R interval of 0 16 second and with rounded P waves are followed by a premature beat with a P R interval of 0 08 second the P wave of which was also upright but had a different more pointed shape The ventricular complex of this beat resembled those of the sinus beats except for being slightly higher After another two sinus beats a premature beat with the same features occurred Longer tracings made it possible to exclude interference between sino auricular and atrio ventricular rhythm and auricular extrasystoles could be ruled out by the shortened P R intervals A V extrasystoles seems the correct explanation The lower tracing shows that conduction to the ventricles of such premature beats was blocked if they followed the preceding beat with a shorter

coupling in such instances isolated P waves were recorded after the T waves of the preceding beat In both tracings the intervals following the extrasystoles were not compensatory and the intervals be tween the extrasystolic and post extra systolic P waves equalled that between two normal sinus beats

Multiple A V extrasystoles

Occasionally A V extrasystoles occur in succession forming shorter or longer groups In the electrocardiogram such ectopic beats show ventricular complexes of supraventricular form preceded by P waves which are inverted in the leads discussed above and having shortened P R intervals

Fig 57a shows an example of two such series interrupted by one normal sinus beat The P R intervals of the extra systoles measure 0 12 second as compared with the 0 17 second of the sinus beat The first extrasystole of the second series shows marked aberration of the ventric ular complex and its P R interval is longer (0 2 second) than that of the other extra systoles The factors responsible for dis turbances of conduction affecting the first of a series of extrasystoles were discussed in connexion with those of ventricular and auricular origin (*see* pp 39 and 60) Such extrasystoles in groups form a transition to short runs of paroxysmal tachycardia An example of this in which exercise increased the rate of the A V tachycardia is discussed in the section on paroxysmal tachycardia (Scherf and Weissberg *see* p 237)

Fig 57b reproduces a group of nine A V extrasystoles with preceding activa tion of the auricles presumably originat ing in the upper part of the A V node The whole paroxysm is shown including sinus beats before and after it The P R interval of the sinus beats was 0 20 second that of the A V beats 0 16 second The first A V beat occurred prematurely the last was followed by a post extrasystolic interval

Fig 58 was obtained from a young

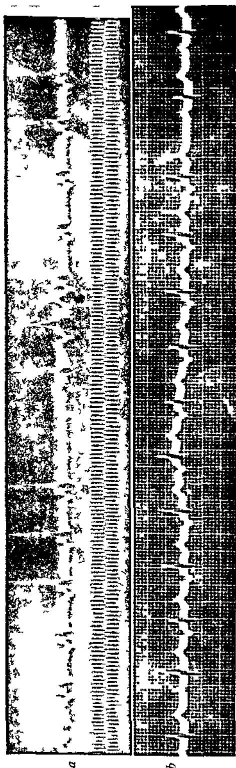


Fig 57 —Both tracings lead 2 obtained from different patients Multiple A V extrasystoles (short paroxysms of A V tachycardia)

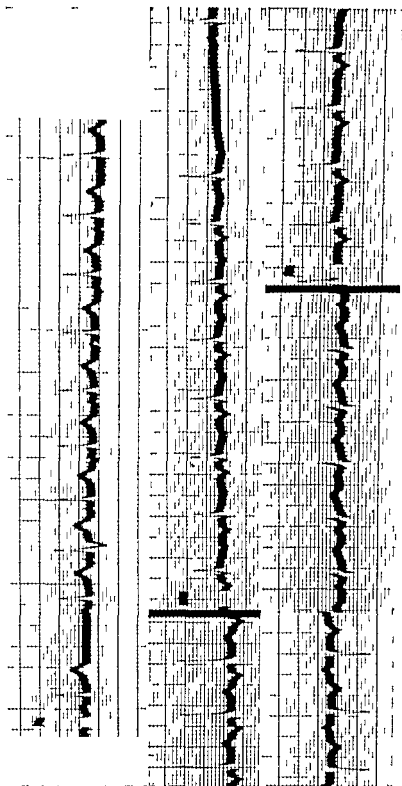


Fig 58—Top tracing lead I middle leads 2 and 3 bottom leads aVR aVL and aVF Multiple A V extrasystoles

man without any evidence of structural heart disease Lead 1 shows a paroxysm of supraventricular tachycardia with aberration of the first extrasystole The deep sharply inverted P waves in leads 2 3 and aVF and the upright P waves in leads aVR and aVL strongly suggest that the ectopic beats originated in the A V node

Fig 59 illustrates the unusual combination of a coronary sinus and a ventricular extrasystole

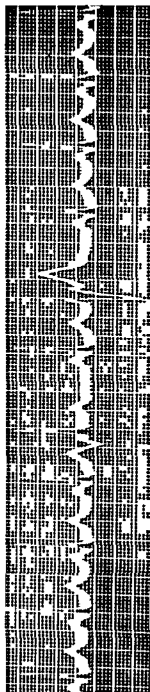


Fig 59 —Lead 2 Combination of a coronary sinus and a ventricular extrasystol

Clinical significance

A V extrasystoles are rare Not infrequently they are erroneously diagnosed in cases of auricular extrasystoles whose P waves are indistinct or buried in the final deflection of the preceding beat

A V extrasystoles have the same significance as ventricular and auricular ones Since in the A V variety the flow of blood from auricles into ventricles is more seriously impaired than is the rule with the two other types it results in a larger quantity of blood being thrust back into the veins which in some patients gives rise to a particularly unpleasant kind of palpitation

SUMMARY

Our conceptions about the site of origin within the A V node and the diagnostic criteria of A V extrasystoles are based on observations on A V rhythm It is pointed out that with the impulse arising in the A V node the contraction of auricles and ventricles occurs more nearly simultaneously than with any other site of impulse formation A V rhythm and A V extrasystoles were subdivided according to whether activation of the auricles precedes coincides with or follows that of the ventricles The foundation of the view is briefly stated that these different sequences of activation indicate origin of the impulse in the upper middle or lower portions of the A V node respectively The mechanism of these three varieties is diagrammatically illustrated The electrocardiographic features of the several kinds of A V extrasystoles are discussed and illustrated by examples The attempts at separating a coronary sinus rhythm from upper nodal A V rhythm are critically discussed and it is concluded that such distinction is not possible with any degree of certainty This is due to the effect of disturbances of conduction upon the electrocardiogram of A V extrasystoles which is discussed in some detail including reports of cases of A V extrasystoles with blocked conduction to auricles as well as to ventricles The complicating factors introduced by disturbances of conduction have resulted in doubts about the possibility of deducing from the electrocardiographic features the site of origin within the A V node of A V beats A suggested revised classification is discussed which distinguishes A V rhythm and A V extrasystoles (a) with preceding

auricular (b) with simultaneous auricular and ventricular and (c) with preceding ventricular activation

While we do not intend to offer any final opinion on this subject reasons are given for our view that a distinction between impulse formation in the upper (including coronary sinus area) and lower portions of the A V node is possible with a fair degree of probability

Instances of A V extrasystoles in groups (multiple A V extrasystoles) are described The clinical aspects of this arrhythmia are briefly discussed

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SINUS EXTRASYSTOLES

It is a well recognized fact that in the mammalian heart centres with the highest degree of spontaneous impulse formation are least prone to produce extrasystoles and vice versa The commonest site of origin of extrasystoles are the ventricles which have the lowest auto maticity Conversely the S A node which owing to its high rate of impulse formation is the normal pacemaker of the mammalian heart gives rise to extrasystoles so rarely that only a very few cases are on record in which the presence of sinus extrasystoles in man can un reservedly be accepted

On the grounds of the time relations in polygraphic tracings this arrhythmia was first reported in man by Wenckebach in 1907 and Rihl in 1913

Experimental Observations

Experimentally the extra contractions elicited from the sinus and the great veins have been studied on numerous occasions and some particular properties were found which are of physiological as well as of clinical interest

One of the earliest investigations is that of Tigerstedt and Stromberg who in 1888 found on the blood filled sinus venosus of the frog s heart that the post extrasystolic interval was not compensatory as had been established for the ventricle by Marey but often shorter Owing to the smallness of the recorded excursions obtained with a primitive method no finer analysis of the time relations was possible In his classical investigations on the frog s heart Engelmann (1896) established beyond doubt that the interval following an extra systole originating in the sinus or the great veins as a rule equalled the interval between two normal contractions With extrasystoles occurring early in diastole the post-extrasystolic interval often was longer than that between two normal beats but with cycle lengths of one to three seconds this lengthening never exceeded 0 2–0 3 second and in fifteen thousand instances observed in over a hundred frogs never reached the degree of making the pause compensatory The later in diastole the extrasystole occurred the smaller the increase in length of the post extrasystolic interval the moment in diastole in which an extrasystole was followed by an interval equalling the normal cycle length varied in different instances Occasionally the post extrasystolic interval was slightly shorter than the interval between two normal beats

The problem was recently re examined by Emery and Loomis (1943) in the heart of the tortoise By means of a fine thread and carefully equilibrated aluminium lever mechanical records of the beating sinus were obtained and over two thousand tracings analysed While the fundamental fact was confirmed that the post extrasystolic intervals following sinus extrasystoles were never compensatory some details regarding their length were found to differ from those prevailing in the frog s heart If the extra contraction was produced within the first quarter of the cycle the post extrasystolic interval was *always shorter than a normal cycle length* if it *originated in the first third* of the cycle the post extrasystolic interval was shorter than the period between two normal beats in 77 per cent and longer in 9 4 per cent with an extrasystole originating in the middle third of the cycle the corresponding figures for the pause following it were 54 1 and 25 2 per cent respectively and with extrasystoles occurring in the last third of the cycle the post extrasystolic interval was shorter than the normal cycle length in only 8 5 per cent and longer in 80 per cent Contrary to the conditions present in the frog s heart in the heart of the tortoise the earlier in the cycle a sinus extrasystole occurs the shorter the following pause tends to be and with a stimulus applied late in diastole the extra contraction is almost certain to be followed by an interval exceeding in length that between two normal beats A hypodynamic condition of the tortoise modified the time relations owing to the long refractory period of the sinus an extrasystole placed as early as the condition of the

sinus would permit was invariably followed by a longer pause than normal As the length of the refractory period of the sinus was found to vary in different animals individual variations in the length of the post extrasystolic intervals were common

These conditions were found essentially to apply also in the mammalian heart (Cushny and Matthews Hering Lewis 1910 Sansum) and there is general agreement that as far as the disturbance of the normal rhythm is concerned sinus extrasystoles differ fundamentally from extrasystoles originating in any other part of the heart The one dissenting opinion (Hirschfelder and Eyster) may we believe be disregarded in view of the weight of experimental evidence supporting this statement This peculiarity of sinus extrasystoles consists in the fact that the post extrasystolic interval equals or is only a little longer or shorter than that between two normal periods but is never compensatory The explanation is that with an extrasystole originating at the site of impulse formation of the dominant rhythm the next impulse has to be formed anew from the moment of the extrasystole and the time required is on the whole equal to that between two spontaneous impulses For this reason the view has been put forward that it would be possible to deduce from these time relations the site of normal impulse formation (Hering) It has also become clear that the conditions prevailing in the case of sinus extrasystoles provide another proof if such were needed for Engelmann s explanation of the compensatory pause after ventricular extrasystoles namely that the latter is not due to any change in excitability of the heart but simply a period of waiting for the next impulse originating in a different part of the heart whereas a post extrasystolic interval equalling the normal cycle length indicates impulse formation at the same site in which the extrasystole originated This law is not confined to the sinus but holds good for any part of the heart which contains a centre of spontaneous impulse formation for instance the isolated perfused ventricle of the mammalian heart (Woodworth) the auricle in certain fishes (Skramlik) or ventricular extrasystoles in complete A V block

Occasionally sinus extrasystoles may be blocked (Engelmann 1894 Skramlik Emery and Loomis Fig 3A)

The Electrocardiogram

In the electrocardiogram origin of an extrasystole in or near the normal pacemaker is characterized by a premature complex resembling the normal complexes in every respect and in all leads In particular the P waves have the same shape as those of the normal beats (Lewis 1910) and the post extrasystolic interval equals that between two normal beats or is slightly longer or shorter but never compensatory The shortening of the post extrasystolic interval after sinus extrasystoles is considered to be due to lengthening of the time of conduction of the extrasystole from the sino auricular node to the auricles conditions of sino auricular conduction being similar to those of the A V conduction of auricular extrasystoles (*see* p 53) (Wenckebach and Winterberg) Since the activity of the sinus is not noticeable in records this explanation is only an inference though generally accepted Another explanation was put forward by Lewis (1912) namely that the shortening was due to stimulation of physiological impulse formation at the point at which they arise so that the succeeding physiological impulse is formed more rapidly than usual but Lewis himself stressed the rarity of this phenomenon and in the authors opinion differences in the rate of conduction is by far the more likely explanation Slight lengthening of the post extrasystolic interval after a sinus extrasystole may be due to variations in rate of the sinus rhythm and also to some inhibition of impulse formation in the S A node caused by the extrasystole The arrhythmia produced by sinus extrasystoles will as a rule be less marked in the auricles than in the sinus and in some cases less marked in the ventricles than in the auricles (*see also* p 48)

The above electrocardiographic criteria are the strictest that could be laid down for this

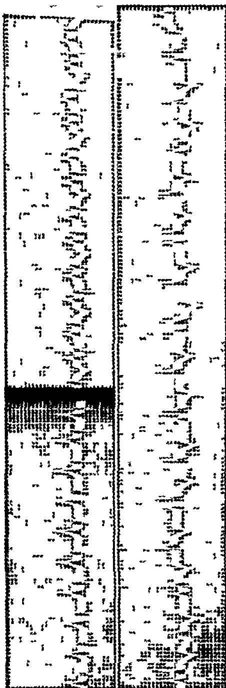


FIG 60—From an experiment on a dog Top tracing Before and after the appearance of sinus extrasystoles elicited by the injection of ouabaine into the head of the sinus node Bottom tracing Sinus extrasystoles precipitated by the injection of ouabaine into the tail of the sinus node For further explanation see text

diagnosis to be made Regarding clinical instances as far as we are aware only two cases reported in the literature satisfy these conditions (Geiger and Goerner Langendorf and Mintz discussed below) It seems doubtful however whether these criteria are not too narrow It is true that absolute identity in appearance in the electrocardiogram of premature and normal complexes strongly suggests an origin of the extrasystole in or very near the sino auricular node but the reverse cannot be said to hold good Altered and even inverted P waves may be found in one or the other lead with premature beats which unquestionably arise in the sino auricular node (Rothberger and Scherf Scherf 1945) Fig 60 provides additional experimental evidence The records were obtained from dogs with the heart *in situ* The upper tracing was recorded during an experiment in which a fresh solution of ouabaine was injected into the area of the head of the sinus node Before the injection the cycle length measured 0 31 second Within six minutes from the injection bigeminal rhythm occurred the extrasystoles originating at the site of injection and having a coupling of 0 25 second and the post extrasystolic intervals measuring 0 34 second While the P waves of both beats of the bigemini have identical shapes they differ from those present before the injection The T waves of those ventricular beats which are preceded by a short diastolic interval are deeply inverted while the QRS complexes remained unchanged In the experiment from which the bottom tracing was obtained ouabaine was injected into the region of the tail of the sinus node Coupled beats resulted the P waves of the sinus beats being upright tall and peaked whereas those of the extrasystoles were triphasic and so shallow as to be almost isoelectric The coupling of the extrasystoles measured 0 36 the post extrasystolic intervals 0 52 second the normal cycle length was 0 48 second as shown by two successive sinus beats at the end of the tracing In both instances reproduced in Fig 60 the post extrasystolic intervals were therefore slightly longer than the normal cycle length

These investigations demonstrate that beats originating in the sinus node may give rise to P waves of a shape different from those of the dominant sinus rhythm either owing to disturbances of intra auricular conduction or to a different site of origin within the sino-auricular node Moreover the post extrasystolic interval may be slightly longer than the normal cycle length Applying this to arrhythmias recorded in man it must be conceded that some degree of differences in shape of the P waves of the premature beats do not necessarily exclude their sino auricular origin for instance the case of Lewis 1912 section 2 and Fig 10

In cases of bigeminal action due to beats of sinus origin the difficulties regarding the diagnosis of sinus extrasystoles are further increased by the fact that various disturbances in impulse formation in the sino auricular node other than sinus extrasystoles and sino auricular disturbances of conduction can produce identical arrhythmias Regarding the latter 3 2 sino auricular block with or without Wenckebach s periods may be mentioned The various mechanisms are clearly illustrated diagrammatically in a paper by Clerc Lévy and Calo

These considerations afford an understanding why the diagnosis of sinus extrasystoles in man can unreservedly be accepted in only very few of the reported instances now to be discussed

Clinical Observations

As already mentioned only two cases reported in the literature satisfy the strictest conditions as described above Geiger and Goerner s patient a man of sixty four with carcinoma of the oesophagus exhibited coupled beats occasionally interrupted by a series of three regular beats of constant rate The complexes of the premature beats were identical in all leads including amplified semi direct chest leads with those of the dominant rhythm The cycle length of the normal beats was 0 96 second the coupling of the premature beats

0 68 and the post extrasystolic intervals 0 96 that is equalled the normal cycle length It was possible in this case to exclude other kinds of sinus arrhythmia for instance simple sinus arrhythmia (phasic respiratory as well as non phasic independent of respiration) sino auricular block and auricular extrasystoles The other instance is Case 1 of Langendorf and Mintz In records obtained from a sixty year old man all leads except lead 1 showed coupled beats P P intervals of 0 98 second alternating with those of 0 80 During the undisturbed rhythm re corded in lead 1 the P P intervals measured 0 98 second that is were of the same length as the long intervals during bigeminal action These time relations make it possible to exclude other arrhythmias of sinus origin with a fair degree of probability and to consider the arrhythmia to be due to sinus extrasystoles with post extrasystolic intervals equalling the normal cycle length

Another possible instance was reported by Schlachman In a man of fifty six with pernicious anaemia he recorded a bigeminal rhythm in which the two beats had identical shape The P P intervals alternated between 0 68 and 0 96 second The bigemini persisted in maximum expiration and during carotid sinus pressure but was absent in maximum inspiration and abolished by amyl nitrite When the number of R B C had risen from 1 580 000 to 3 820 000 only simple sinus arrhythmia was recorded Schlachman s interpretation of the arrhythmia as sino auricular extrasystoles cannot be considered proved as two successive normal beats were never recorded during the arrhythmia and no evidence is given that the first and second beat of the bigemini had identical shape in all leads Moreover the intervals do not allow to exclude sino auricular 5 3 block and the arguments put forward in favour of sino auricular extrasystoles as against S A block are not wholly convincing However this observa tion can be considered as a possible though not proved instance of this rare arrhythmia

As far as it is possible to make a diagnosis from one lead Fig 61 may provide an example of a sinus extrasystole The tracing obtained from a patient with hypertension shows a regular sinus rhythm with a cycle length of 1 36 second Occasionally premature beats occurred resembling in every respect those of the dominant rhythm Their coupling always measured 1 0 second and the post extrasystolic interval 1 32 seconds that is was slightly shorter than a normal period Such extrasystoles were recorded three times in lead 1 whilst they were absent in the other leads

Regarding the case of Lewis (1912) see above

In Laslett s case the records are quite inadequate for an accurate diagnosis of the arrhythmia to be possible A

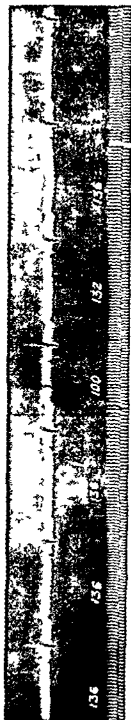


Fig 61 —Lead I The fourth beat is most probably a sinus extrasystole The post-extrasystolic interval is shorter than the cycle length of the normal rhythm

case reported by Wenckebach and Winterberg is better explained by assuming the presence of auricular extrasystoles some of them conducted and some blocked What is regarded by those authors as the normal period seems to include a blocked auricular extra systole shown in the phlebogram by a notch in the descending limb of the *v* waves Schill reported a case of numerous sinus extrasystoles with disturbances of conduction of several kinds but as far as the short reproduced records allow of any analysis the arrhythmia was due to auricular extrasystoles some of them blocked His interpretation of a case of sinus arrhythmia reported by Fogelson as being an instance of numerous sinus extrasystoles is unacceptable as far as the published data make a more detailed diagnosis possible *auricular extrasystoles and periods of paroxysmal auricular tachycardia seem a* far more likely explanation

SUMMARY

The fundamental difference between extrasystoles originating in the sino auricular node and those arising in any other part of the heart consists in the fact that the post extrasystolic interval of the former equals or is only a little longer or shorter than that between two normal periods but is never compensatory The reason for this is discussed and the relevant experimental work is reviewed In the electrocardiogram origin of an extrasystole in or very close to the normal pacemaker is characterized by a premature complex resembling the normal complexes in every respect and in all leads the length of the post extrasystolic interval being as stated above It is pointed out that the above criteria require some extension in certain circumstances In view of the results of experimental work neither a different shape of the P waves of the premature beats provided their P R intervals do not exceed those of the normal ones nor a post extrasystolic interval slightly exceeding the normal cycle length exclude sinus extrasystoles but in such instances an auricular origin of the premature *beats cannot be ruled out The reported cases of sinus extrasystoles in man are* critically reviewed and only very few of them can be accepted as such without reserve While the presence of sinus extrasystoles in man is established their occurrence is extremely rare

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INTERPOLATED EXTRASYSTOLES

Interpolated extrasystoles are those which are interposed between two beats of the dominant rhythm occurring in their usual sequence

In the discussion on ventricular extrasystoles it was pointed out that the normal impulse following the extrasystole usually fails to yield a ventricular contraction because it occurs at a time when the ventricles still are in the refractory period of the extrasystole If however the heart rate is slow and the extrasystole occurs early in diastole the refractory period of the conducting system and of the ventricles may already have terminated by the time the first post extrasystolic sino auricular impulse arrives and a ventricular contraction will follow In these circumstances a ventricular extrasystole will occur between two successive sino auricular beats

Disturbance of Rhythm

Fig 62 illustrates diagrammatically the disturbance of rhythm caused by an inter polated extrasystole The cycle length of the auricular rhythm is assumed to be constantly eighty hundredths of a second Following the second normal beat a ventricular extra systole is assumed to occur with a coupling of 0 28 second The first post extrasystolic beat (Beat No 3) is shown to be conducted to the ventricles with a slightly lengthened atrio ventricular conduction time This results in a lengthening of the interval between the beats preceding and succeeding the extrasystole (that is coupling plus post extrasystolic interval in the ventricular rhythm) assumed in the diagram to amount to 0 04 second The subse quent interval in the ventricular rhythm (between the fourth and fifth ventricular contrac tion) is shortened by that amount

Interpolated extrasystoles are the only variety of extra systoles in the sense of being additional supernumerary beats

It will be shown below that apart from the prevailing sinus rate and the degree of prematurity of the extrasystole other factors are of importance in determining whether a ventricular extrasystole will be interpolated or followed by a compensatory pause

These remarks refer to interpolated ventricular extrasystoles in cases of sinus rhythm It is obvious that interpolated extrasystoles can occur only if the formation of impulses in the centre of the dominant rhythm is unaffected by the extrasystole Therefore interpolated extrasystoles usually originate in a chamber of the heart other than that containing the centre of impulse formation of the dominant rhythm that is in the mammalian heart in the ventricle in the heart of certain fishes and reptiles (where the centre of normal impulse formation is situated in the separate sinus) in the auricle or ventricle In the mammalian heart in exceptional circumstances (*see* below) interpolated extrasystoles may originate in

the same chamber in which the centre of impulse formation of the prevailing rhythm is located namely interpolated auricular extrasystoles or interpolated ventricular extra systoles in complete A V block

Regarding observations in a case of interpolated A V extrasystoles (Bix) *see* section on Atrio ventricular Extrasystoles p 73

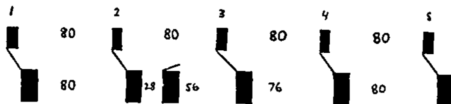


FIG 62 —Diagram illustrating the disturbance of rhythm caused by an interpolated extrasystole The figures indicate intervals in hundredths of a second (except the top row which indicates consecutive numbers of S A beats) For explanation see text

Interpolated ventricular extrasystoles during sinus rhythm

This is the only variety which though by no means common occurs with any frequency in man and is of any clinical significance

Interpolated ventricular extrasystoles may have first been observed by Galen and by Senac (*see* historical remarks) and possibly by Marey (Busquet Dresbach and Munford) though this is denied by others (Myers and White) They were certainly often seen experimentally and correctly interpreted [Loven Engelmann Kaiser Woodworth Rihl 1904 Trendelenburg (frog) Bethe (caput medusae)] In man they were first described by Wenckebach in 1899 on the grounds of an analysis of the radial pulse only (*see* also Wenckebach 1903 1906) His interpretation was subsequently confirmed by means of venous pulse tracings by Pan (1903 and 1904) and further descriptions soon followed (Volhard Gerhardt Laslett Staehelin and Nicolai Dresbach and Munford Myers and White)

Amongst 5 000 electrocardiograms obtained in the Massachusetts General Hospital from 2 392 patients in the course of six years ventricular extrasystoles occurred in 284 tracings from 200 patients Of these twenty four tracings obtained from fourteen patients showed interpolated extrasystoles that is 7 per cent of the patients exhibiting ventricular extrasystoles (Myers and White)

Fig 63 reproducing a record from a fifty nine year old man with syphilitic aortic incompetence shows signs of left ventricular hypertrophy and myocardial damage (slurred QRS complexes deep notched Q waves in lead 3 and abnormal final deflections) Interpolated ventricular extrasystoles occurred in every second diastole although the rate of the sinus rhythm was as high as eighty Only in lead CR-4 was one extrasystole followed by a compensatory pause

The atrio ventricular conduction of the post-extrasystolic beat after interpolated extrasystoles often is delayed particularly with higher rates (Pan Mackenzie *see* also Figs 63 and 64) Lengthening of the P R intervals of these beats was found in about 50 per cent of the cases and intervals as long as 0 78 second have been reported The subsequent diastole is correspondingly shortened In some cases the P R interval of the second post extrasystolic beat also may be prolonged (Katz *et al*) Moreover aberrant intraventricular conduction of the post extrasystolic beat is not uncommon in some instances only changes in the T wave occur (*see* Fig 65a) more frequently the QRS complex shows



Fig. 63.—The three standard leads and lead CR 4. Interpolated ventricular extrasystoles in every second diastole except for the second extrasystole in lead CR 4 which is not interpolated.

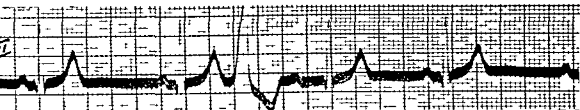


Fig. 64.—Changes in the first post-extrasystolic beat after an interpolated extra systole. Lead 2. Lengthening of the P R interval to 0.28 sec. as compared with 0.16 sec. of the sinus beats.

marked anomalies (*see* Fig 65b) Occasionally several post extrasystolic beats may be affected (*see* Fig 66) These changes in the features of the post extrasystolic beat(s) are due to disturbances of conduction resulting from an incomplete recovery of the conducting system after the greater demands made upon it by the two preceding beats following one another at a short interval This is easily understood in the case of extrasystoles originating above the bifurcation and being conducted to the ventricles via the normal paths But even in the far commoner case of an interpolated extrasystole originating below the bifurcation it has to be assumed that it is conducted over a certain distance through specialized



FIG 65 —Changes in the first post-extrasystolic beat after an interpolated extra systole *a* affecting the T wave *b* affecting the QRS T complex

fibres (*see* p 373) The distance can only be a short one as only a short time interval separates the interpolated extrasystole from the post extrasystolic beat It is unlikely that such retrograde conduction should go further than the A V node

Ashman by way of explaining the lengthening of the P R interval of the post extrasystolic beat without any alteration of its ventricular complex pointed out that if the extra systole is conducted in a retrograde direction to the A V node the delay in the conduction of the post extrasystolic beat takes place in the A V node with the result that by the time the impulse reaches the bundle branches and their ramifications their recovery is already complete A different explanation put forward by Straub in 1918 that the lengthening of the P R interval of the post extrasystolic beat is due to a greater latency of the ventricles is now generally discarded

The above considerations tend to show that very small changes in the time sequence of extrasystole and post extrasystolic impulse will determine whether an extrasystole is interpolated or followed by a compensatory pause In addition to the rate of the prevailing sinus rhythm and the degree of prematurity of the extrasystole the rate of recovery of conductivity and excitability also will be of importance that is the length of the refractory period for the duration of which vagal tone is (amongst others) a decisive factor This affords an understanding for the observation that of ventricular extrasystoles occurring in the same phase of diastole some may be interpolated whereas others are not sometimes in the same tracing without any change in the sinus rate extrasystoles may paradoxically be followed by a compensatory pause though they occurred earlier in diastole than interpolated ones (Wenckebach and Winterberg p 179)

Two interpolated extrasystoles within one diastole have been described (Pan 1904) but so far as we are aware this phenomenon has not been recorded electrocardiographically It is not uncommon however that two (*see* Fig 67) and rarely even three extrasystoles may replace one normal beat so that one or two respectively of these extrasystoles could be considered interpolated

Clinical Significance

Isolated single interpolated ventricular extrasystoles have the same clinical significance and produce the same symptoms as any other type of extrasystole If however an interpolated extrasystole occurs after every normal beat over a certain period the ensuing sudden doubling of the ventricular rate may easily be misinterpreted as paroxysmal tachycardia (Gerhardt) or auricular flutter

Fig 68 shows two instances of this kind of arrhythmia In the top tracing (Fig 68a) the ventricular rate rose during the occurrence of the interpolated extrasystoles from about 72 to about 144 and the post extrasystolic beats showed marked aberration of the QRS complexes in the bottom tracing (Fig 68b) the interpolated extra systoles caused a rise in the ventricular rate from 59 to 118 and the A V conduction time of the post extrasystolic beats was lengthened Interpolated extrasystoles have therefore to be included amongst the conditions which may give rise to a sudden doubling of the ventricular rate the commonest cause of this seems to be auricular flutter with sudden change in the degree of block or paroxysmal tachycardia may be responsible

Blanc reported an unusual observation in a man of fifty seven suffering from syphilis and attacks of angina pectoris in whom inter polated extrasystoles were recorded after every second beat only during the anginal attacks

Pulse Changes

In the case of interpolated extrasystoles characteristic pulse changes may occur which can be of diagnostic help

Owing to the marked prematurity of the extrasystole its stroke volume often is so small that it does not produce a palpable pulse at the wrist The pulse produced by the post extrasystolic beat usually is smaller than the normal one (owing to a partial emptying of the ventricles by the extrasystole and interference by the extra systole with diastolic filling) and as a result of delay in conduction of the post extrasystolic beat and the prolonged pre sphygmic time associated with the smaller stroke volume the pulse wave of this beat reaches the wrist with a certain delay The subsequent pulse on the other hand has a larger volume since a longer time interval was available for the diastolic filling between the post extrasystolic and the subsequent beat as compared with the interval between the extrasystole and the post extrasystolic beat moreover as the interval following the post extrasystolic beat is somewhat shortened the second pulse following an interpolated extrasystole will be felt after a slightly shorter interval The changes produced by an interpolated extrasystole will therefore consist of the sudden occurrence of a

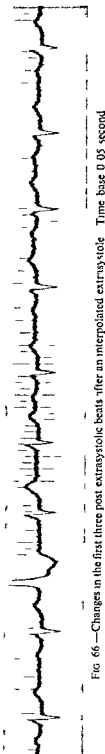


FIG 66 —Changes in the first three post extrasystolic beats after an interpolated extrasystole Time base 0 05 second

smaller pulse occurring with a slight delay followed by a larger pulse occurring after a slightly shortened diastole This sequence can be of some diagnostic significance (Lian and Jonas) Owing to the features described the pulse produced by a series of interpolated extrasystoles may give the impression of being a *pulsus alternans* it has been termed *pulsus pseudoalternans* by Myers and White

Interpolated Auricular Extrasystoles

It has been pointed out above that interpolated extrasystoles are far more likely to originate in a chamber of the heart other than that containing the pacemaker of the domin ant rhythm Thus in fishes and reptiles in which the normal pacemaker is situated in the separate sinus interpolated auricular extrasystoles are not uncommon (Lovén Skramlik Trendelenburg 1909) and they are occasionally seen also in frogs in spite of the slow rate of retrograde conduction in amphibia In the mammalian heart on the other hand in which auricular extrasystoles are either followed by a compensatory pause or more com monly are conducted to the sino auricular node where they discharge the immature normal impulse interpolated auricular extrasystoles can occur only in exceptional circumstances

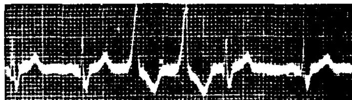


FIG 67 —Two ventricular extrasystoles replacing one sinus beat

Thus Kisch described interpolated auricular extrasystoles in the dying rabbit heart and their occurrence was explained by the assumption that the damaged tissue failed to conduct in the usual way the extrasystole which thus failed to reach the sinus node Direct leads from the auricular muscle proved the presence of partial contractions

Interpolated auricular extrasystoles in the dog were found by Drury and Brow in six out of ten animals Auricular extrasystoles were produced by means of induction shocks the electrodes being at a distance of 0 5 to 1 cm from the sinus node In some experiments the rate of stimulation was but slightly higher than the spontaneous rate with the result that some extrasystoles occurred very early in diastole and reached the sinus node very shortly after the discharge of its preceding impulse As the refractory period of the sinus node is considerably (about 30 per cent) longer than that of the auricular muscle some extrasystoles reached the sinus node while still in the refractory stage This was found to be the case if the extrasystolic impulse arrived at the sinus node 0 22 second after the dis charge of the last preceding impulse It is obvious that the long duration of the refractory period of the sinus node is a pre requisite for auricular extrasystoles to be interpolated According to Drury and Brow only if this exceeds the normal sino auricular conduction time plus the refractory period of the auricle plus the time required for the retrograde conduction of the extrasystole to the sinus node will an auricular extrasystole be interpolated

Interpolated auricular extrasystoles were also seen experimentally by Eccles and Hoff

No case of interpolated auricular extrasystoles in man has yet been published in which the diagnosis could be accepted unreservedly by us In a case published by Rihl (1926) in which this diagnosis was put forward for the first time another interpretation was conceded by the author himself since the auricular periods during which the possibly

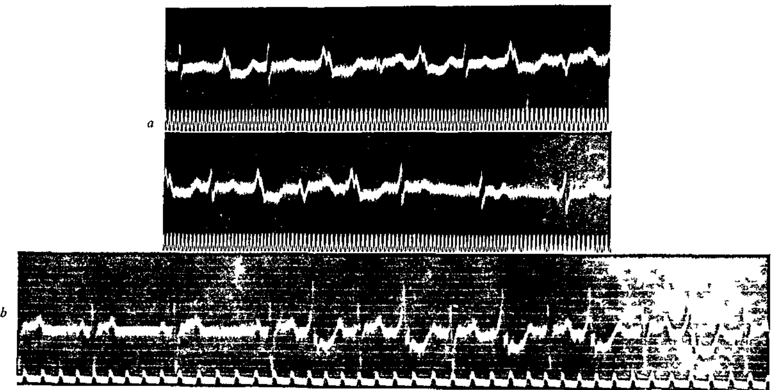


FIG 68 —Two instances of interpolated ventricular extrasystoles occurring in bigeminal form resulting in a sudden doubling of the ventricular rate *a* The two strips are continuous Time base 0 04 sec *b* Time base 0 2 sec

interpolated auricular extrasystoles occurred were consistently shorter than the normal periods *moreover the P waves of the beats following the extrasystoles had abnormal* shapes Cases published by others actually represent multiple auricular extrasystoles (Calabresi Reid) In the tracings of Burghard and Wunnerlich artefacts simulated the arrhythmia Weinberg and Katz s case is not convincing because it can be explained by the presence of auricular extrasystoles in a case with bizarre but not unusual T waves in the chest leads A case described in detail by Wenckebach and Winterberg (p 193) shows how easily successive auricular extrasystoles may be mistaken for interpolated auricular extra systoles Normal P waves of the beats preceding and following the auricular extrasystole have to be postulated in addition to the appropriate time relations for a diagnosis of inter polation to be made In this respect the most convincing case so far is that published by *Gonczy and Gyorgyi The tracing obtained from a patient with rheumatic mitral valvular* disease showed the occurrence of a premature auricular systole followed by a beat with a P wave of the same shape as that of the other sino auricular beats and occurring at the normal time Longer tracings however showing the post extrasystolic rhythm would be necessary to establish the diagnosis with certainty It may be mentioned in passing that polygraph tracings are inadequate for the diagnosis of this arrhythmia as they give no

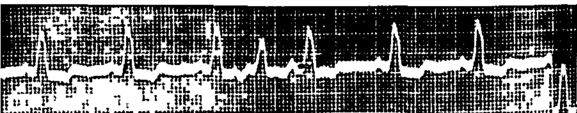


FIG 69 —Lead I The third sinus beat is followed by two auricular extra systoles though the possibility of an interpolated auricular extrasystole can not be definitely excluded

indication about the site of origin within the auricle of the impulse of the post extrasystolic beat such information however is indispensable in order to exclude an ectopic origin of the post extrasystolic beat and thus to exclude multiple auricular extrasystoles

Fig 69 illustrates the difficulties in interpretation even from the electrocardiogram The first three beats are sinus beats showing the features of left bundle branch block with cycle lengths of 0 85 and 0 87 second respectively The third sinus beat is followed by an auricular extrasystole with slight aberration of intra ventricular conduction The diagnostic difficulty arises in respect of the next beat (the fifth of the record) since the P wave of this beat may be interpreted as being that of a normal sinus beat or as indicating a second auricular extrasystole If the former interpretation is accepted the preceding auricular extrasystole would be an interpolated one The identity in shape of the P wave of this beat with that of the P waves of the sinus beats would be in favour of this view On the other hand the interval between the P waves of the beats preceding and succeeding the auricular extrasystole (that is the interval between the P waves of the third and fifth beats) measures 0 91 second and is thus distinctly longer than the cycle length of the sinus rhythm The most probable conclusion therefore is that the fifth beat is also an auricular extrasystole and that the third sinus beat is followed by two auricular extrasystoles in succession but an inter polated auricular extrasystole cannot be excluded with certainty in this instance

Therefore while interpolated auricular extrasystoles have experimentally been demon strated in the mammalian heart their occurrence in man cannot yet be considered as established

Interpolated Ventricular Extrasystoles in Idio-Ventricular Rhythm (complete Atrio-Ventricular Block)

In man ventricular extrasystoles occurring in complete heart block are nearly always followed by an interval equal to that between two idio ventricular beats (*see* p 96) The obvious explanation is that the extrasystoles originating in the same chamber as the impulses of the dominant ventricular rhythm are conducted to the centre of impulse formation of the idio ventricular beats where they discharge the immature impulse For the same reason interpolation will occur only in exceptional circumstances in such cases

Interpolated ventricular extrasystoles in the automatically beating ventricle were seen by Woodworth Hofmann and Holzinger and Koch While it is possible that this was due to partial contractions of the ventricle or its hypodynamic state it is more likely that the underlying mechanism was a protective block (discussed on p 168) of the idio ventricular centre

In man a case of interpolated ventricular extrasystoles in complete heart block and auricular fibrillation was described by Weiser in a digitalized patient The ventricular periods measured 1 5 second the period which contained the extrasystole 1 55 second The slight lengthening of this period was attributed to an inhibitory effect of the extra systole on the formation of the next stimulus this explanation however seems unlikely



FIG 70 —Lead 2 Complete heart block with ventricular extrasystole which did not disturb automatic ventricular rhythm this is protectively blocked The extrasystole is interpolated From SCHERF and BOYD *Clinical Electrocardiography* Wm Heinemann London

as the extrasystole being interpolated could not have reached the centre In some of the cases of interpolated ventricular extrasystoles with auricular fibrillation and A V block (Frey Fahrenkamp Wolferth) a similar lengthening (by 0 06-0 07 second) of the period containing the extrasystole was found (Wolferth)

A good example of interpolated ventricular extrasystoles during sinus rhythm and complete heart block was described by Scherf and Boyd (*see* Fig 70)

SUMMARY

Interpolated extrasystoles are defined as those which are interposed between two beats of the dominant rhythm occurring in their usual sequence The disturbance of rhythm caused by this variety is described and diagrammatically illustrated The only variety which occurs with any frequency and is of any clinical significance is the occurrence of interpolated ventricular extrasystoles during sinus rhythm This variety is described in some detail and illustrated by examples The first post extrasystolic beat is often conducted with some delay which has to be located in the A V node The clinical significance of interpolated extra systoles is on the whole the same as that of non interpolated ones only if one interpolated extrasystole follows each beat of the dominant rhythm over longer periods may a sudden doubling of the ventricular rate ensue The pulse changes produced by an interpolated extrasystole are described and their mechanism analysed It is pointed out that as a rule

interpolated extrasystoles originate in a chamber of the heart other than that containing the pacemaker of the dominant rhythm In the mammalian heart therefore interpolated auricular extrasystoles can occur only in exceptional circumstances some of which reported in the literature are briefly discussed Instances of this arrhythmia reported to have b en observed in man are critically reviewed and it is pointed out that no such case can be accepted unreservedly and that the occurrence of this arrhythmia in man cannot be con sidered as established

A personal observation is described in which this possibility has to be conceded though the interpretation favoured by us is that the record in question demonstrates two auricular extrasystoles following in succession Interpolated ventricular extrasystoles in complete A V block occur only in exceptional circumstances the few reported instances experi mental and clinical are briefly reviewed

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EXTRASYSTOLES ORIGINATING IN THE STEM OF THE BUNDLE OF HIS

Extrasystoles originating in the stem of the bundle of His—stem extrasystoles for short—are in one sense ventricular ones Owing to their arising above the bifurcation of the bundle however they differ from the common varieties of ventricular premature beats in this one important respect that they spread through the ventricles along the same paths as supraventricular beats While they have this in common with A V nodal extrasystoles they differ from these and resemble the great majority of the common ventricular ones in that the auricles continue to be activated by the S A node This is due to the blocking of the retrograde spread of the extrasystoles to the auricles which takes place in the A V node It follows that stem extrasystoles cannot be differentiated from A V nodal ones with blocked retrograde conduction to the auricles

The diagnosis of stem extrasystoles is based on the following electrocardiographic features a premature beat occurred the ventricular complex of which has in all leads the same shape as those of the supraventricular beats there is undisturbed sequence of the P waves the P wave related to the premature beat has in all leads the same shape as those of the supraventricular beats the post extrasystolic intervals are compensatory

The P wave related in time to the premature beat—that is the P wave of the normal sinus impulse with blocked conduction to the ventricles—may precede its ventricular complex with a shortened P R interval (Lewis Fig 1) or (more frequently) follow it In the latter case it is visible between the QRS and T wave of the premature beat (Lewis Fig 2 Lewis and Allen Holzmann)

Extrasystoles with this site of origin are very rare In many textbooks they are not even mentioned and the number of published cases is very small One case each was reported by Lewis and by Lewis and Allen in both such origin was considered probable and we would associate ourselves with this interpretation In the first of these instances the diagnosis seems correct particularly in view of the record reproduced in the author s Fig 12 In the latter the necessity of assuming aberration of intra ventricular spread introduces a

difficulty without however disproving the interpretation offered Wenckebach and Winterberg reproduce a record interpreted as A V extrasystoles with blocked conduction to the auricles which as stated above in this section could equally well be considered as showing stem extrasystoles Two instances fulfilling the above diagnostic criteria and interpreted as stem extrasystoles have been published by Holzmann

Fig 71 provides an example of a probable instance of a stem extrasystole The record showed the features of left bundle branch block with lengthening of the P R intervals Periodically premature beats were recorded which had in all leads the same shape as the sinus beats The post extrasystolic intervals were compensatory P waves of the sinus impulse with blocked conduction to the ventricles were not visible in the reproduced or in any of the other leads but they invariably occurred at a time when they were buried in the QRS complex of the extrasystole

To our knowledge oesophageal leads have not yet been recorded in this type of extra systoles This would be essential to clarify the question of retrograde conduction of such beats to the auricles

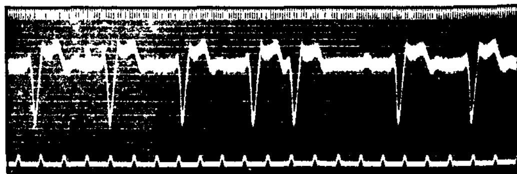


FIG 71 —Lead 3 Left bundle branch block with lengthening of the P R intervals The extrasystole (fifth beat) is not preceded by a P wave and has the same shape as the sinus beats The post-extrasystolic interval is compensatory The extrasystole originated probably in the stem of the bundle of His Upper time base 0 02 second lower 0 2 second

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EXTRASYSTOLES IN COMPLETE A V BLOCK

Introductory Remarks

In addition to their clinical importance extrasystoles occurring in complete A V block present features of special physiological interest since they illustrate some aspects of the mechanism underlying normal impulse formation and conduction

In the great majority of cases of extrasystoles observed in man they originate in a part of the heart which is anatomically or functionally separate from that containing the pace maker of the dominant rhythm But if extrasystoles occur in complete A V block in which

the ventricles are stimulated by impulses originating in a ventricular centre the extra systoles and the automatic beats arise in the same part of the heart and a disturbance of rhythm results which differs from that observed in the more common kinds of ventricular extrasystolic arrhythmias

Experimental Observations

This phenomenon has been extensively studied experimentally While a brief reference can be found in a paper by Cushny and Matthews in 1897 the first detailed investigation of the effect of extrasystoles upon the rhythm of the automatically beating mammalian ventri cle was carried out by Woodworth in 1902 on the perfused apex of the dog s ventricle He established the fact that the interval following an extra contraction was not compensatory but approximated the interval between two spontaneous beats being as a rule slightly shorter than the normal cycle (94 1 per cent) and tending to be shorter the earlier in diastole the extra contraction occurred In some of his experiments (for instance his Fig 5) the degree of shortening is so great that doubts seem justified whether his interpretation of some of his tracings is acceptable as only mechanical records were obtained the possibility of two or more extrasystoles following the stimulus cannot be excluded

Hering (1905a) pointed out that the length of the post extrasystolic interval in the iso lated mammalian ventricle usually equalled the normal cycle length and that the same conditions prevailed as in extrasystoles elicited from or very near the pacemaker of the dominant rhythm that is the *sinus venosus* or great veins of the frog s heart or the orifices of the great veins of the mammalian heart In all such cases the extrasystole arising in or very close to the centre of origin of the dominant rhythm there destroys the immature impulse of the next automatic beat approximately the same time is required for the next impulse to become effective as elapses between two automatic beats so that the post extra systolic interval equals the normal cycle length Hering therefore recommended using these time relations in order to test by means of extra stimuli whether in a given experi ment the centre of automatic impulse formation is situated in the ventricles Hering s reasoning was that only if the post extrasystolic interval equals or is slightly shorter than the normal cycle length is it certain that automatic ventricular rhythm is present Post extrasystolic intervals slightly longer than the spontaneous periods also occur in idio ventricular rhythm but do not prove its presence since they may be caused by ventricular extrasystoles with retrograde conduction to the auricles For a discussion of the older literature *see* Rihl

With the advent of electrocardiography such measurements as advocated by Hering have become unnecessary for the purpose of ascertaining the presence or otherwise of idio ventricular rhythm but the underlying principle would still be of considerable general physiological interest if such time relations were confined to ventricular extrasystoles in complete A V block as Hering thought This however is not the case since similar time relations may be present in partial A V block

The effect upon the ventricular rhythm of ventricular extrasystoles in partial A V block is not uniform and Erlanger s statement (1906) that it is the same as in complete A V block cannot be accepted as valid for most cases The post extrasystolic intervals in partial A V block may as in cases of complete A V block equal the normal cycle length Wertheimer has demonstrated that if in frogs a 2 1 block is induced by means of barium chloride and an auricular or ventricular extrasystole is produced by an induction shock the length of coupling of the ventricular extra-contraction + the post extrasystolic interval often equals the length of three auricular cycles whilst the post extrasystolic interval equals the normal cycle length In such cases the length of the post extrasystolic interval may lead to the erroneous conclusion that an automatic ventricular rhythm is present unless the auricular contractions are also recorded Actually in Wertheimer s experiments the ventricular

contractions were initiated by the normal pacemaker throughout but as a result of the ventricular extrasystole a permanent shift of the ventricular rhythm occurred If however owing to a more persistent impairment of conduction the subsequent auricular impulse also fails to be conducted and the length of the coupling + the post extrasystolic interval therefore *equal the length of four auricular cycles the post extrasystolic interval becomes compen* satory and no permanent shift of the ventricular rhythm takes place since the original ventricular rhythm is resumed with the first post extrasystolic beat In some but not all cases of this kind the post extrasystolic interval is slightly shorter than compensatory owing to increased speed of conduction of the post extrasystolic beat this being due to the longer period of recovery provided by the long post extrasystolic interval

To return to conditions in complete A V block the salient fact is that the post-extra systolic interval in the automatically beating ventricle equals or closely approximates the normal cycle length The one dissenting report about the occurrence of true compensatory pauses in such circumstances (Rothberger and Winterberg) is explained by the high ventricular rate and the long distance between the focus of origin of the extrasystoles and that of the automatic ventricular rhythm in their experiments and does not invalidate the above statement Regarding the exact length of the post extrasystolic intervals some differences were found in different species and under different experimental conditions as briefly mentioned above In the isolated frog s ventricle it was found to be somewhat longer than the normal cycle length and the lengthening increased with the degree of prematurity in diastole of the extrasystole (Hofmann and Holzinger) In the automatically beating mammalian ventricle on the other hand the post extrasystolic interval often equals the normal cycle length or may be a little longer or shorter but is never compensatory (Hering 1905a Erlanger Hofmann and Holzinger)

By reducing the concentration of NaCl to 0 5–0 2 per cent or by increasing the concentration of KCl in the Locke solution an inhibitory action of extrasystoles upon the following beat could be produced in the automatically beating mammalian ventricle when this had not been present before this effect was shown to be directly due to the electrolytes and not to differences in the rate of flow (Hofmann)

It can therefore be said that extrasystoles in the automatically beating ventricle produce a permanent disturbance of the ventricular rhythm the post extrasystolic interval being equal to or somewhat longer or shorter than the automatic cycle length but never compensatory in nature or (with rare exceptions) in length Shortening of this interval may be explained either by a stimulating effect of the extra contraction analogous to conditions prevailing in some cases of auricular extrasystoles (*q v*) or to the same mechanism which is responsible for the shortening of the post extrasystolic interval after sinus extrasystoles (*see* pp 79 *seq*)

In the mammalian heart and in clinical observations lengthening of the post extrasystolic interval in such cases is far more common than shortening and has to be ascribed to an inhibitory action of the extrasystole upon the impulse formation of the following automatic beat (*see* section on Auricular Extrasystoles pp 47 55) In dogs in which complete heart block was produced by clamping the A V bundle the degree of the inhibitory effect upon the ventricular action of ventricular extrasystoles was shown to depend on the rate and duration of the stimulation and on the condition of the heart (Erlanger and Hirschfelder) similar conditions were demonstrated in cats with asphyxial heart block (Lewis and Oppenheimer) The clinical importance of these findings will be discussed later in this section

Clinical Observations

Whereas in man auricular extrasystoles in complete A V block are very rare (Brown, Deglaude and Zade Holzmann Katz) ventricular extrasystoles are relatively common (Hoesslin) This is understandable in view of the fact that conditions which are known to

be common causes of A V block are also prone to give rise to ventricular extrasystoles for example coronary sclerosis or diphtheria and amongst drugs digitalis It is also evident that a lesion which by being situated in a portion of the conducting system causes block is also likely to cause extrasystoles since they originate in the same kind of tissue They may occur so frequently as to produce bigeminal rhythm

Fig 72 was obtained from a sixty nine year old woman with complete A V block and Stokes Adams attacks The Wassermann reaction was positive The patient was given ephedrine grain ½ thrice daily The record shows complete A V dissociation the P waves being bifid The cycle length of the automatic ventricular rhythm was constantly 1 50 seconds the post-extrasystolic interval measured 1 53 seconds

Fig 73 was obtained from a fifty two-year old patient with coronary sclerosis admitted with pulmonary oedema He was given digitalis and complete A V block occurred in the course of treatment The interval between the first two automatic beats was 1 16 seconds After the second automatic beat two extrasystoles occurred which were followed by an interval of 1 33 seconds The interval following the next extrasystole measured 1 28 seconds This record illustrates extrasystoles in complete A V block followed by post extrasystolic intervals moderately longer than the normal cycle length This lengthening was more pronounced in the interval following two successive extrasystoles than in that following a single one which is in accordance with the experimental observations quoted above

In man a pronounced shortening of the post extrasystolic interval in complete block is rare but has occasionally been found (Naish Frey)

In patients with A V block the automatic beats (*see* Gilchrist and Cohn) and also the extrasystoles may show varying forms in the electrocardiogram (Scherf Scherf and Schott) In a certain proportion of such cases an automatic beat following an extrasystole shows the same shape as the preceding automatic beat and it is this observation which made it possible to decide that the varying form is due to a change in the site of impulse formation and not to disturbances of conduction of the extrasystolic impulse This conception which also has a bearing

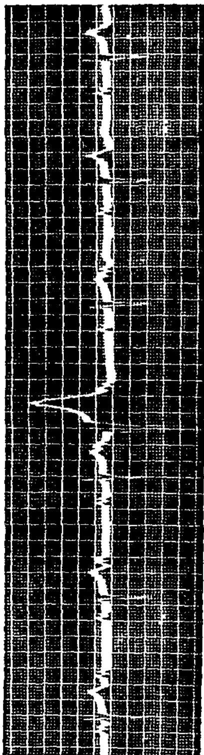


Fig 72 —*Lead CR 2* Ventricular extrasystole in complete A V block

on the differentiation between automatic and extrasystolic impulse formation (*see* p 492) is in accordance with experimental findings on the activity of several centres of impulse formation in the ventricles after severing both branches of the bundle of His (Wilson and Herrmann) Clinically the combination of complete or partial A V block with bundle branch block is by no means uncommon In such cases both bundle branches are affected the A V node and main bundle being found normal histologically This localization of degenerative lesions is due to the fact that the A V node and bundle derive their



FIG 73—Lead 2 Ventricular extrasystoles in complete A V block with lengthening of the post extrasystolic periods

blood supply from a source different from that of the blood supply of the bundle branches (Yater Cornell and Claytor) The presence of active foci in both main branches renders the prognosis more grave

Fig 74 recorded in a seventy five year old patient provides an example The tracing shows complete A V block The first two ventricular complexes were directed upwards the initial portions being widened to 0 11 second and the R R interval being 1 16 seconds The second beat was followed after an interval of 0 68 second by an extrasystole the main deflection of which was directed downwards and the two subsequent automatic beats had the same shape as the extrasystoles the cycle length had increased to 1 28 seconds and the duration of the initial ventricular deflections to 0 16 second



FIG 74—Lead 2 Ventricular extrasystole in complete A V block followed by automatic ventricular beats of the same shape as the extrasystole indicating change in the site of origin of the idioventricular beats

As a rule extrasystoles in complete A V block tend to increase the low ventricular rate and were therefore considered to be a compensatory phenomenon (Frey) In some cases however the depressing effect upon the idioventricular rhythm of the extrasystoles predominates to such an extent that long periods of ventricular standstill with loss of consciousness ensue (Cohn and Lewis Hecht) particularly if groups of successive extrasystoles occur so that this mechanism has to be included amongst the rarer causes of Adams Stokes attacks

The increase in the degree of block in cases of partial heart block resulting from auricular

extrasystoles is mentioned in the appropriate section (p 55) The rare instances of inter polated ventricular extrasystoles in complete A V block are discussed in the section on interpolated extrasystoles

SUMMARY

If ventricular extrasystoles occur in complete A V block the conditions differ from those present in the more common kinds of ventricular extrasystolic arrhythmias as both the extra systoles and the automatic beats of the dominant rhythm originate in the same part of the heart In such cases the post extrasystolic intervals equal or closely approximate the normal cycle length but with very rare exceptions are not compensatory The exact length of the post extrasystolic interval differs in different species and also depends on the experimental conditions Clinically the occurrence of ventricular extrasystoles in complete A V block is not uncommon this is attributable to the fact that the same conditions which are com mon causes of complete A V block are also prone to give rise to ventricular extrasystoles As a rule such extrasystoles tend to increase the low ventricular rate but in some cases their depressing effect upon the idioventricular rhythm is so pronounced that long periods of ventricular standstill ensue and this mechanism has to be included amongst the rarer causes of Adams Stokes attacks

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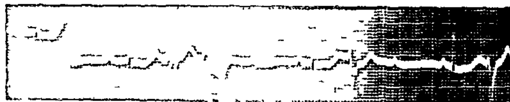


FIG 73—Lead [illegible] Ventricular extrasystoles in complete A V block with length[illegible] of the [illegible] extrasystolic periods

[illegible] supply from a source different from [illegible] of the blood supply of the bundle branches [illegible] Cornell and Claytor) The presence o[illegible]tive foci in both main branches renders [illegible]rosis more grave

F[illegible] 74 recorded in a seventy fi[illegible] patient provides an example The tracing [illegible] complete A V block The [illegible] tricular complexes were directed upwards the initial portions being widened [illegible] d[illegible] and the R R interval being 1 16 seconds The second b[illegible] was followed aft[illegible] of 0 68 second by an extrasystole the main deflection of which was directed downwards and the two subsequent automatic beats had the same shape as the extrasystol[illegible] cycle length had increased to 1 28 seconds and the duration of the initial ventricular def[illegible] to 0 16 second

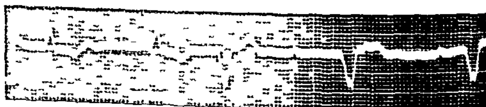


FIG 74—Lead 2 Ventricular extrasystole in complete A V block followed by automatic ventricular beats of the same shape as the extrasystole indicating change in the site of origin of the idioventricular beats

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EXTRASYSTOLES IN A V RHYTHM RETURN EXTRASYSTOLES

Return extrasystoles are produced by an excitation wave which spreads from one cham ber of the heart to another returns to that portion of the heart in which the impulse had first originated and proceeds to give rise to a further systole This phenomenon has been observed mainly in A V rhythm with preceding activation of the ventricles in which the stimulus originated in the ventricular portion of the A V node thence activating ventricles as well as auricles and that portion of the impulse which activates the auricles returning or sending a subsidiary impulse back to the ventricles Similarly a ventricular extrasystole which is reversedly conducted to the auricles may give rise to a return extrasystole, by the return of the impulse to the ventricles probably in or near the A V node

Experimental studies relating to return extrasystoles are intimately connected with those concerned with the effect of extrasystoles upon A V rhythm and it seems appropriate first to discuss this latter subject and subsequently to proceed to that of return extrasystoles

Ventricular or Auricular Extrasystoles in A V Rhythm

Hering (1910) was the first to investigate the effect upon A V rhythm of ventricular and auricular extrasystoles in the mammalian heart Changes in the sequence of and time inter vals between auricular and ventricular contractions were interpreted as indicating a shift in the pacemaker but since only mechanical records were obtained his investigations are mainly of historical interest The same can be said about that part of Ganter and Zahn s extensive investigations on A V rhythm which deals with the effect of extrasystoles

Rothberger and Winterberg s investigations carried out in 1912 marked a considerable advance In their experiments on dogs these authors recorded electrocardiograms in addition to mechanical records of auricle and ventricle moreover the conditions of their experiments were far more physiological than those of Hering Whereas the latter author produced A V rhythm by scorching the sino auricular node Rothberger and Winterberg obtained it by stimulating the left accelerans nerve The main results of their experiments were to determine that after one or several *ventricular* extrasystoles the post extrasystolic intervals tended to be compensatory Occasionally intervals shorter than compensatory were observed Even in cases in which ventricular extrasystoles were reversedly conducted to the auricles compensatory post extrasystolic intervals occurred This latter observation was difficult to understand since it has to be assumed that during its retrograde conduction the extrasystolic impulse passed the A V node there destroying the next immature impulse and producing a permanent shift of rhythm The preservation of the original A V rhyth micity in spite of a retrograde ventricular extrasystole was then considered to be due either to the fact that the extrasystole failed to reach the centre of stimulus formation in the A V node (thus being protectively blocked) or that it produced inhibition of the formation of the next A V impulse Rothberger and Winterberg considered the second alternative as far more likely In the experiments with *auricular* extrasystoles those which were *not* con ducted to the ventricles did not affect the A V rhythm and the post extrasystolic intervals in the auricular rhythm were therefore compensatory If auricular extrasystoles were produced which *were* conducted to the ventricles the post extrasystolic intervals of the ventricular

rhythm either equalled the normal cycle length or owing to inhibition of the formation of the next A V impulse were longer than the normal cycle length but not compensatory in both cases the conducted auricular extrasystole passed through the A V node and thereby produced a permanent shift of rhythm

The use of the word compensatory to describe the length of the post extrasystolic interval in arrhythmias of this kind might well be considered unfortunate as Lewis White and Meakins pointed out in a similar context For restoration of the original rhythm if it occurs comes about in a totally different manner to that described by Engelmann in observing the effect of ventricular extrasystoles upon S A rhythm It would not be due to the control of the post extrasystolic interval by a dominant rhythm but to a balance between the lengths of coupling and post extrasystolic interval respectively such balance being largely coincidental

Lewis White and Meakins reinvestigated this problem on a large scale in experiments on dogs in which A V rhythm was produced by cooling the *sulcus terminalis* both vagi were cut In their experiments the type of A V rhythm was the one with preceding activation of the auricles P waves preceding the QRS complexes In connexion with the subject of the present section their most important findings were With *ventricular* extrasystoles which in most instances were conducted to the auricles the post extrasystolic interval in the ventricular rhythm exceeded that in the auricular rhythm by the sum of the R P interval of the extrasystole and the P R interval of the post extrasystolic A V beat The post extrasystolic interval in the auricular rhythm would accurately represent the interval between the disturbance of the A V impulse formation by the extrasystole and the completion of the next A V impulse if conduction is at the same rate from node to auricle for the two beats which bound it Any divergence should be expected to be in the direction of shortening since owing to its prematurity the R P interval of the extrasystole should be relatively longer Actually with one exception the post extrasystolic interval in the auricular rhythm was longer than the normal P P cycle length With *auricular* extrasystoles the post extrasystolic intervals in the ventricular rhythm had approximately the same length as the R R cycles of the A V rhythm but usually were slightly longer and only exceptionally shorter From these observations particularly those regarding the length of the post extrasystolic intervals in the ventricular rhythm after auricular extrasystoles Lewis White and Meakins drew far reaching conclusions they doubted the validity in such cases of Wenckebach s views about the paramount importance of the speed of conduction of the excitation in accounting for various phenomena in cardiac pathology for instance the lengthening of the P R interval in cases of first degree of heart block the mechanism underlying dropped beats and the length of the post extrasystolic interval after auricular extrasystoles in cases of normal sino auricular rhythm Lewis and his collaborators who did not consider disturbances of conduction in the bundle of His as a possibility argued that if Wenckebach s views were applied in regard to the post extrasystolic intervals in A V rhythm those of the ventricular rhythm after auricular extrasystoles should either equal or be shorter than the R R interval of the A V beats but not be longer as was mostly the case

This objection was proved to be invalid and conditions prevailing in extrasystolic arrhythmias in A V rhythm were further clarified by the work of Scherf and Shookhoff (1925) In their experiments on dogs A V rhythm was produced by severing both vagi and the right accelerans nerve supplemented if necessary by clamping the sino auricular node In most experiments quinine was given intravenously with the double purpose of avoiding ventricular fibrillation and uniformly enhancing the degree of disturbance of conduction so as to facilitate the appraisal of the kind and degree of changes in rhythm Extrasystoles were produced by induction shocks

Fig 75 provides an example of such an experiment The first three beats show A V rhythm with simultaneous activation of auricles and ventricles the P waves being buried

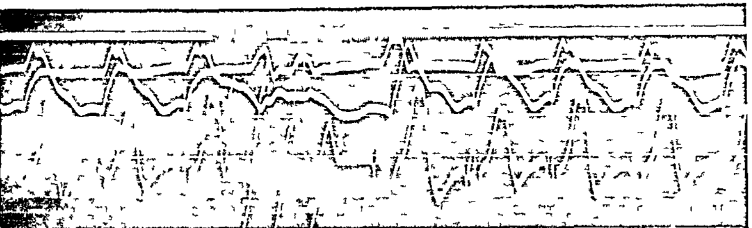


FIG 75.—From an experiment on a dog. From above downward: Signal (electrical stimulation), suspension curves of right auricle and right ventricle, electrocardiogram (ano-oesophageal lead), time base (0.02 second). The first three beats are A V beats with simultaneous activation of auricles and ventricles. After three ventricular extrasystoles elicited by induction shocks inverted P waves appeared before the QRS complexes of the following A V beats. Gradual restoration of the previous condition.

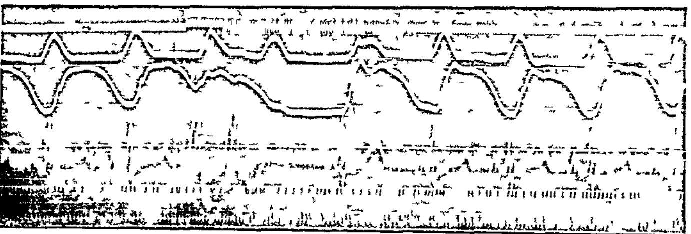


FIG 76.—From an experiment on a dog. Significance of the several tracings as in previous figure. Temporary disappearance after two ventricular extrasystoles of P waves in A V rhythm.

in the ventricular complexes After three ventricular extrasystoles the first two of which the suspension curves show to have been conducted to the auricles whereas the last one remained confined to the ventricles the first post extrasystolic beat shows an inverted P wave preceding the QRS complex at almost a normal P R interval In the following beats the inverted P waves gradually approach the ventricular complexes until the former state of simultaneous activation is re established Fig 76 taken from another experiment shows in the first two beats A V rhythm which differs from that illustrated in the preceding Fig in that the auricles are activated first P waves preceding the QRS complexes Two ventricular extrasystoles are shown which were both conducted to the auricles In the first post extra systolic beat no P wave is visible which indicates simultaneous activation of auricles and ventricles the subsequent beats showing the return of P waves at increasing P R intervals until the conditions prevailing before the extrasystoles were restored

Analysis of the records obtained in numerous experiments showed that in A V rhythm a temporary change in position of the P waves relative to the QRS complexes as a result of ventricular extrasystoles is entirely dependent on and therefore indicates the importance of speed of conduction in the ventricles of the first few post extrasystolic impulses which is itself dependent upon the demands made previously upon the conducting system by the extrasystoles These conditions are diagrammatically illustrated in Fig 77 In Fig 77a and b A V rhythm originating in the lower portions of the A V node is assumed the ventricles being activated before the auricles since regarding the effects of extrasystoles the same conditions prevail in cases of simultaneous activation of auricles and ventricles the origin of the impulse assumed to be in the middle portion of the A V node these two diagrams illustrate the findings in tracing Fig 75 With these two kinds of A V rhythm the temporary occurrence of a positive P R interval after extrasystoles was found only if the last extrasystole was *not* conducted backwards to the auricles (Fig 77a) It could be concluded that this phenomenon is due to delayed conduction of the post extrasystolic beats (particularly the first one) from the A V node to the ventricles This is a result of the fact that the last extrasystole though not conducted to the auricles had travelled through a portion of the conducting system in the ventricles thereby shortening the time of recovery of that portion On the other hand if the last ventricular extrasystole *was* conducted to the auricles (Fig 77b) the time available for recovery of the ventricular portion of the conducting system was not shortened if anything it was slightly lengthened (owing to some inhibition of impuls formation in the A V node caused by the traversing extrasystole) and the phenomenon of a temporary shift of the P waves is therefore never observed in such circumstances In cases of A V rhythm with preceding activation of the auricles in which a positive P R interval is present and the impulse is assumed to originate in the upper portions of the A V node the conditions governing a temporary shift of the P waves after ventricular extrasystoles are the reverse of those discussed in connexion with lower and middle A V nodal rhythm In the diagram Fig 77c and d upper nodal rhythm is assumed and it is shown that only if the last extra systole *was* conducted backwards to the auricles will the P wave of the first post extrasystolic beat temporarily merge with the QRS complex and in the next few beats gradually resume its original position (*see* Fig 76) It could be concluded that this is due to the longer time of recovery available for the portion of the conducting system between A V node and ventricles (*see* Fig 77c) If the last ventricular extrasystole was *not* conducted to the auricles (Fig 77d) the time of recovery of the bundle not only is not longer but shorter and the first post extrasystolic impulse will therefore be conducted to the ventricles at the same speed or more slowly but certainly not faster than before Consequently the moment of activation of the ventricles will not approach that of the auricles that is the P R interval will not become shorter but will remain unaltered or be lengthened and the phenomenon of a temporary merging of the P waves with the QRS complexes will not be observed All these effects of ventricular extrasystoles in the various forms of A V rhythm as well as those of

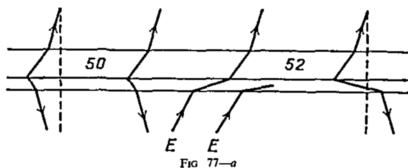


Fig 77—a

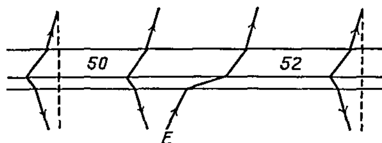


Fig 77—b

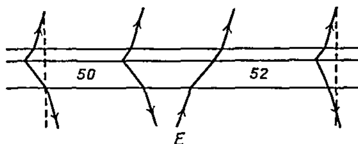


Fig 77—c

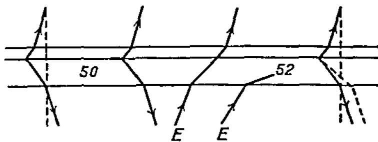


Fig 77—d

Fig 77—Diagram illustrating the effect in A V rhythm of ventricular extra systoles upon the sequence of activation of auricles and ventricles For explanation see text

auricular extrasystoles demonstrated clearly that contrary to the opinion of Lewis White and Meakins the formulae of rest and recovery or want of rest and recovery not only fully account for these phenomena but find a valuable support in the results of such investigations In A V rhythm relatively small alterations in the speed of conduction of the impulse to auricles and ventricles result in comparatively large alterations in the time sequence of auricular and ventricular systole since in A V rhythm the spread of the excitation wave to those portions of the heart takes place in opposite directions (*see* Scherf and Shookhoff 1926a) Actually a temporary change of position of the P waves relative to the QRS complexes after extrasystoles is clearly seen in several of the records reproduced by Lewis White and Meakins and of Rothberger and Winterberg but was not commented upon by the writers

Clinically as far as we are aware this phenomenon has only once been clearly observed by Edens (his Fig 12) although differently explained by him The tracing shows A V rhythm with inverted P waves preceding the QRS complexes An extrasystole occurred but it is impossible to decide from the rather indistinct reproduction whether it was an A V extrasystole with preceding activation of the ventricles or a ventricular extrasystole with retrograde conduction to the auricles In the first post extrasystolic beat no P wave is visible but reappears in the second one with a shortened P R interval the original condition being restored with the fourth post extrasystolic beat Another possible instance is Fig 18 of the paper of Weil but dissociation with interference seems the more likely explanation in this case

It might be argued that the conditions described in this section are not sufficiently important to warrant a detailed description We make no apology for having done so for what matters is not the change in the detailed time relations and not whether or where a P wave or any other wave is found in the records but the knowledge that can be derived from such changes regarding general principles of cardiac physiology and pathology To quote a few of those points

It could be demonstrated that disturbances of conduction exist in that part of the conducting system which is situated between the A V node and the myocardium without either of these structures being involved This made it possible to disprove alternative explanations which had been put forward in order to explain the above described and allied phenomena for instance a change in the latency of the A V node (Mobitz) or of the myocardium (Straub) or of the rate of conduction in the A V node (Lewis *et al*) The unsatisfactory conception of shifting of the pacemaker was proved to be unnecessary for the explanation of such arrhythmias in which this phenomenon was postulated In addition Scherf and Shookhoff s work showed the wide range of applicability of Engelmann s and Wenckebach s conceptions of the importance of changes in the rate of conduction of impulses dependent on the period of rest for and recovery of the conducting system in accounting for various features in cardiac pathology (some of which are detailed above p 103) Another conclusion of general importance which could be drawn from such experiments is that impulses which do not yield a contraction of any portion of the heart may yet exert a profound influence on the cardiac rhythm by travelling through and causing fatigue of a part of the conducting system Such investigations proved also to be one of the most instructive examples illustrating the great importance of what Engelmann with such vision had termed in 1896 the method of the extrasystoles (Methode der Extrasystolen) namely the use of extrasystoles for the elucidation of many diverse problems in cardiac physiology and pathology Lastly a knowledge of the conditions prevailing in A V rhythm and its disturbances by extrasystoles is indispensable for an understanding of the mechanism underlying return extrasystoles which on their part throw light on the mechanism of origin of some kinds of extrasystolic arrhythmias

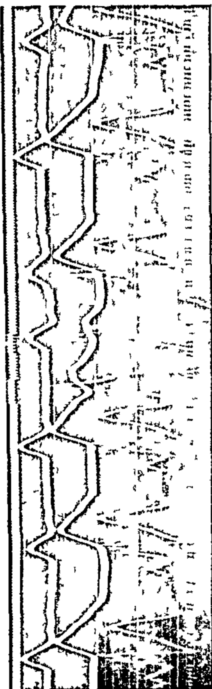


FIG 78 —From an experiment on a dog Significance of the several tracings as in Fig 75 The sixth beat is a return extrasystole precipitated by the preceding ventricular extrasystole For further explanation see text

Return Extrasystoles

Experimental Investigations

The subject which was extensively investigated experimentally by Scherf and Shookhoff (1926b) may be introduced by Fig 78 A V rhythm had been produced in the way described above (p 103) The first three beats are A V beats with preceding activation of the auricles diphasic and widened P waves preceding the initial complexes with a P R interval of 0 11 second The R R intervals measure about 0 5 second The shape and width of the P waves as well as the notching and widening of the R waves are due to quinine (p 290) These three beats are followed by two ventricular extrasystoles the second of which is reversedly conducted to the auricles with a V A interval of 0 22 second The following beat has in its RS and T portions all the appearances of the initial A V beats and calculated from the suspension curves follows the last extrasystole at about 0 3 second This beat occurs far too early to be of A V origin for the interval between the last extrasystole (which by being reversedly conducted to the auricle was bound to destroy on its passage through the A V node the immature A V impulse) and the following beat should at least equal the R R intervals of the A V beats or owing to inhibition of impulse formation in the A V node be longer but certainly not be shorter The explanation seems to be that this beat is due to the impulse which precipitated the last extrasystole and which on its way to activate the auricle returned to activate the ventricle a second time The presumed mechanism is diagrammatically illustrated in Fig 79 This interpretation is strongly supported by the observation that the premature beats appeared *only* if the ventricular extrasystole caused by an induction shock was conducted back to the auricle if several ventricular extrasystoles occurred this phenomenon was only observed if the last extrasystole was conducted to the auricle This kind of extrasystole is one variety of what has been termed by the authors return extrasystoles

Another set of circumstances in which return extrasystoles could be produced in the dog s heart were certain instances of A V rhythm with preceding activation of the ventricles namely that form in which an inverted P wave follows the QRS complexes In all such

experiments it could be demonstrated that return extrasystoles occurred whenever and only if the conduction of the A V impulse to the auricle was sufficiently delayed for the returning impulse to reach the ventricles after the end of the refractory phase

Several methods were found effective to produce these phenomena (Scherf 1941) Fig 80 provides an example of one of them A V rhythm was produced by clamping the sinus node the suspension curves showed that the auricles contracted at a short interval after the ventricles and in the electrocardiogram inverted P waves followed the QRS complexes By electrically stimulating the conus of the right ventricle a series of extrasystoles were elicited the last five of which are shown at the beginning of the figure Subsequently the retrograde conduction (R P) intervals alternated between 0 05 and 0 09 second and it can be seen that a premature beat of supraventricular origin occurred only and always with the longer R P intervals Within a few seconds longer R P intervals ceased to occur and pre mature beats were no longer observed These findings can be explained by assuming that as a result of the series of extrasystoles fatigue of the conducting system ensued with consequent alternation of the R P conduction times and that after the longer R P intervals the impulse returning from the auricles to the ventricles reached the latter when they had become again excitable Fatigue of the conducting system by means of auricular extra systoles had the same result



Fig 79 —Diagram illustrating the mechanism of origin of the beats as recorded in the previous figure

Fig 81 illustrates a similar phenomenon A V rhythm was produced in a similar manner that variety being present in which auricles and ventricles are activated simul taneously Five extrasystoles were elicited in the right ventricle by means of induction shocks Here again this resulted in an alternation of the ventriculo auricular conduction times as shown by the suspension curves only the beats with the longer V A intervals were followed not only by one but by two premature beats Analysis of the electrocardiogram and suspension curves warrants the conclusion that the first return extrasystole is conducted backwards to the auricles and as a second return extrasystole is again conducted to the ventricles Accurate measurements of the various P R and R P intervals are not possible in this record but approximate figures taken from the suspension curves show that the P R interval of the first return extrasystole is about 0 24 second while the conduction time of its reversed conduction to the auricles measures only 0 14 second the P R interval of the second return extrasystole is only about 0 13 second When after a few seconds alter nation of the ventriculo auricular conduction times ceased return extrasystoles failed to occur but could be made to re appear several times by again producing series of ventricular extrasystoles by means of induction shocks

Another method to produce return extrasystoles during A V rhythm consists in stimu lation of the vagus thereby lengthening the R P intervals In Fig 82 which is taken from such an experiment the R P intervals varied between 0 09 and 0 13 second and it can be seen that a return extrasystole occurred whenever the R P interval exceeded 0 12 second The R P interval of the first beat measured 0 11 second that of the second 0 13 second and this beat is followed by a return extrasystole with a P R interval of about 0 09 second The R P intervals of the following beats were 0 09 0 12 **0 13** 0 09 0 10 0 11 **0 13** second

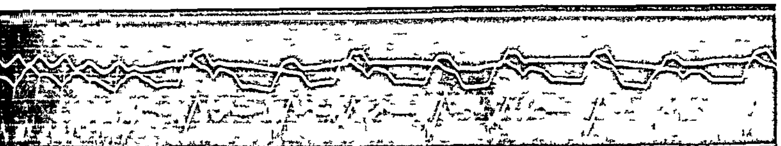


Fig 80 —From an experiment on a dog Significance of the several tracings as in Fig 75 The beginning of the record shows the last five of a series of ventricular extrasystoles elicited by electrical stimulation of the conus of the right ventricle Subsequently A V rhythm with alternation of the R P intervals ensued those beats with the longer R P intervals being followed by a return extrasystole



Fig 81 —From an experiment on a dog Significance of the several tracings as in Fig 75 After a series of ventricular extra systoles elicited by electrical stimulation of the right ventricle A V rhythm with alternation of the R P intervals ensued those beats with the longer R P intervals being followed by two return extrasystoles in succession

those beats which were followed by a return extrasystole being indicated by bold figures Owing to their prematurity the return extrasystoles were aberrantly conducted in the ventricles as evidenced by their different shape in the electrocardiogram The R R intervals of the A V beats following in succession without extrasystoles were 0 60-0 62 second those containing an extrasystole measured 0 71 0 70 and 0 69 second respectively so that the return extrasystoles were interpolated This is only possible if the centre of impulse formation in the A V node was not affected by the extrasystoles That this was the case is also proved by the fact that the P P intervals remained practically the same throughout varying only between 0 61 and 0 68 second It has to be assumed that a protective block of the A V centre of impulse formation existed owing to which the return extrasystoles did not interfere with A V impulse formation Moreover this is another instance of an arrhythmia in which the disturbance of conduction is situated in the part of the conducting system between A V node and ventricle in the instances of return extrasystoles conduction through this portion of the system took place three times within a short time and owing to the inadequate period of recovery conduction to the ventricles of the post extrasystolic beat was delayed This resulted in a shortening of the R P interval particularly of the first post extrasystolic beat The assumption of a conduction of the extrasystole through a different path is not warranted Failure of auricular stimuli which are conducted to the ventricles to disturb the activity of the A V nodal centre has also been noted by Lewis, White and Meakins and by Rothberger and Winterberg

Lastly warming of the A V node by means of a thermode or depression of the sinus node by various means elicited return extrasystoles Here again these occurred only if the activation of the auricles took place with a sufficient delay after that of the ventricles Thus with the former method return extrasystoles were only observed if the R P intervals measured at least 0 12 second with the latter 0 18 second was the shortest R P interval with which return extrasystoles occurred not only resulting in bigeminy but occasionally also in trigeminy two return extrasystoles following in succession (Scherf 1947)

In all these experiments and those discussed in the preceding pages return extrasystoles appeared exclusively and also constantly when the R P interval attained a certain length This finding strongly supports the interpretation given The question arises whether a certain degree of delay in the retrograde conduction to the auricles of A V beats or ventricular extrasystoles alone gives rise to return extrasystoles or whether in addition fatigue vagal stimulation and similar factors are necessary the authors favour the first alternative

Clinical Observations

In order for a diagnosis of return extrasystoles (reciprocal beats) to be made in clinical cases it has to be ascertained that the auricular contraction which in its turn gives rise to the second ventricular one is due to the retrograde activation of the auricles by an impulse which originated in the A V node (unless the return extrasystole was elicited by a ventricular extrasystole with retrograde conduction to the auricles) This means that the underlying rhythm is A V nodal rhythm with preceding activation of the ventricles and that the auricular stimuli do not arise in an independent focus for example the sino auricular node For if the latter is the case the condition would be dissociation with interference an arrhythmia in which a faster A V rhythm co exists with a slower sino auricular rhythm with occasional interference of the A V rhythm by conducted sino auricular beats (*see* p 178 *also* Herrmann and Ashman) In the electrocardiogram a reciprocal beat manifests itself by the presence of A V rhythm a P wave which is inverted in leads 2 and 3 following the QRS complex at a certain distance such P wave being followed in its turn by a supraventricular QRS complex after an interval consistent with the assumption that the second ventricular beat is due to the return of this auricular impulse to the ventricles Such inverted P waves are therefore sandwiched in between two supraventricular QRS complexes (White 1921)

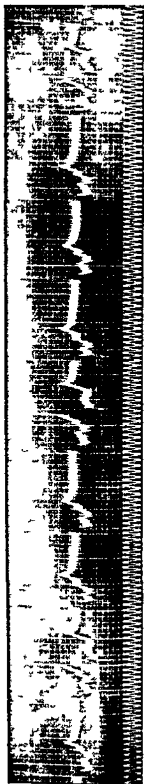


Fig 82 —From an experiment on a dog A V rhythm Those beats which as a result of vagal stimulation had a lengthened R P interval were followed by a return extrasystole

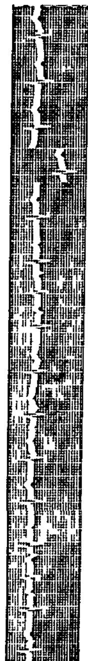


Fig 83 —Lead 2 A V rhythm In two places two return extrasystoles in succession (the third and fourth and tenth and eleventh beats) For further explanation see text

Fig 83 provides an example obtained from a fifty six year old man with coronary sclerosis The underlying rhythm is A V rhythm with gradually lengthening R P intervals During undisturbed A V rhythm the R R intervals measured 0 66 second (rate 91) and the record shows that whenever the R P interval reached 0 22 second the P waves were followed by a QRS complex which in relation to the underlying A V rhythm occurred prematurely There is no evidence in this record of an independent sino auricular or auricular pacemaker The interpretation that these premature ventricular beats are return extrasystoles is supported by the observation that the speed of orthograde conduction of such beats varied inversely with that of the preceding retrograde one Thus the R P interval of the second beat measured 0 22 second and the P R interval of the following (conducted) beat 0 28 whereas the corresponding figures of the next beat were R P 0 3 P R 0 20 The tracing therefore demonstrates return extrasystoles of which two occurred in succession in two places (the third and fourth and tenth and eleventh beats) This arrhythmia due to two successive return extrasystoles is even rarer than single return extrasystoles the only reported clinical observation of this kind is Case 5 of Decherd and Ruskin (1943) who termed this sequence triplets Another possible instance is the case of von Dobozy though differently interpreted by him In his Fig 4 two groups each of three beats were recorded Dobozy s explanation is that the first two beats of each group were an A V beat with a return extrasystole the R P intervals being 0 45 and 0 46 respectively and that the last beat of each group was a supraventricular extrasystole An alternative and more likely explanation seems to be that each group consists of an A V beat followed by two return extrasystoles Such an interpretation would be supported by the presence between the second and third beats of the first triplets of a differently shaped inverted P wave the absence of such a wave at the corresponding place in the second group would not exclude the same rhythm (cf Cutts and Levin s findings discussed below) The fact that the P R intervals (0 16 second) of the last beats of each group were shorter than those of the first return extrasystoles would be analogous to Scherf s experimental findings (*see* Fig 81)

The number of published clinical observations in which the diagnosis of return extra systoles can be considered established is very small In an extensive review of this problem Decherd and Ruskin collected twenty two cases up to 1943 to which they added three personal observations The first case was published by White (1915) A V rhythm was present and whenever as a result of carotid sinus pressure or the exhibition of digitalis the R P intervals were prolonged to about 0 3 second bigeminy resulted Amongst various explanations White discussed the mechanism of a return of the impulse The same author reported a second case in 1921 showing a bigeminal action with R P intervals of 0 4 and P R intervals of 0 18 The diagnosis however seems less certain since the P waves were upright when bigeminy was first observed and when subsequently they became inverted bigeminy did not always occur when the R P interval reached the same length Drury first used the term reciprocal rhythm in a clinical observation in which he described this rhythm during attacks of A V tachycardia with incomplete retrograde block and a rate of about 150 Other cases in which this arrhythmia can be considered established are Bishop in whose case return extrasystoles occurred after atropine Gallavardin and Gravier and Katz and Kaplan who demonstrated transient reciprocating rhythm during carotid sinus pres sure Case 1 of Blumgart and Gargill (although the tracing is too short to be conclusive some of the authors observations in this case regarding the effect of exercise atropine etc make the diagnosis of return extrasystoles probable the other three of their four cases are unacceptable) Dock (though some of the tracings seem better explained by the assump tion of dissociation with interference for instance his Fig 5) Reid in a child of ten five years after diphtheria though not interpreted as such by the author Cutts one case *see* below Gravier Froment and Guiran (R P 0 45 P R 0 2) though the varying direction of the P waves made some of the tracings difficult to interpret with certainty (*see* below)

Levin (1941) one case *see* below Decherd and Ruskin three cases Tournaire Deyrieux and Augier (observed after every second A V beat with a R P interval of 0 3 atropine shortened this interval to 0 22 and abolished the return extrasystoles) Langendorf (1948) and Pick and Langendorf (same case) de Mesquita Case 2 Grau and Gouaux (during a terminal ventricular tachycardia in a man of seventy six with congestive heart failure due to arteriosclerosis on one occasion two return extrasystoles were recorded also fusion beats) Bix (Case 3) Holzmann (1952)

Some special features warrant a brief discussion Generally the R P (Q P) intervals were longer than the P R intervals of the return extrasystole (for instance White 1915 Gravier *et al* Decherd and Ruskin) which conforms with the observation that generally retrograde conduction takes place less readily in the mammalian heart than the orthograde one (*see* Retrograde Conduction of Extrasystoles p 126) there are however exceptions (for example Blumgart and Gargill Case 1) An inverse relationship between the R P and following P R intervals seems to be the rule In Decherd and Ruskin s extensive study of one of their cases these time relations were used to determine the curve of recovery of conductivity This showed the presence of a period of relative refractoriness which resembled recovery curves obtained in experimental work and in a human case of heart block by Ashman and Herrmann It was also found that in general reciprocal beats occurred with longer R P intervals which is in accordance with the experimental findings described above but Cutts pointed out that in some tracings R P intervals were not followed by reciprocal beats as long as or longer than R P intervals followed by typical reciprocal beats This observation also made by Tournaire *et al* tends to show that apart from the length of the preceding R P interval other factors determine whether return conduction occurs or fails this recalls similar considerations concerning interpolated extrasystoles (*q v*) Cutts also noted that the QRS complex of the second beat of the couple often differed somewhat in shape from the first which is attributable to aberrant conduction of the second impulse in the ventricles

The spread to the ventricles of a return extrasystole may be completely blocked and its presence is then deduced from the time relations between two successive A V beats If such interval without a recorded ventricular contraction of a return extrasystole equals that in which a return extrasystole was recorded in the ventricular rhythm the assumption is justified that such lengthening in the interval between two successive A V beats was caused by a return extrasystole which owing to blocked conduction to the ventricles failed to yield a ventricular contraction (concealed conduction Langendorf Pick and Langendorf Fleischmann)

Regarding the effect of drugs digitalis was often noted to cause or increase the number of reciprocating beats (White Dock Blumgart and Gargill Case I Decherd and Ruskin Cutts) Vagal stimulation by carotid sinus pressure produced transient reciprocating rhythm (Gallavardin and Gravier Katz and Kaplan) or increased their number (Blumgart and Gargill Case 1) but in the last case physostigmine had no effect Statements about the effect of atropine are conflicting in Bishop s case it provoked return extrasystoles and in that of Dock greatly increased their number the A V rhythm being accelerated with lengthening of the R P and slight shortening of the P R intervals whereas in Case I of Blumgart and Gargill 2mg completely abolished the return extrasystoles Cutts found that atropine alone had no constant effect regarding reciprocating rhythm but in one instance abolished it when given after digitalis According to Decherd and Ruskin grain 1/50 given intravenously accelerated retrograde conduction while producing little effect on the refractory period or forward conduction Quinidine prolonged refractoriness and delayed both retrograde and orthograde conduction

Clinical observations of return extrasystoles elicited by ventricular extrasystoles with retrograde conduction are very rare Fig 84 provides an example The record was obtained from a seventy three year old patient with hypertension and coronary sclerosis It

shows sinus bradycardia the R R intervals measuring 1 02–1 27 seconds (rate 47–58) Groups of two ventricular extra systoles are seen the first fourth and fifth of which were followed by a compensatory pause The second and third of these groups on the other hand were followed by a post extrasystolic interval which was very much shorter and in which an inverted P wave is seen The R P intervals that is in this case the interval between the beginning of the second extrasystole of the groups and the inverted P wave measured about 0 4 second the P R intervals of the post extrasystolic beats 0 2 second (equalling that of the sino auricular ones) The conclusion is warranted that the second extrasystole of the second and third groups were followed by a return extrasystole

Fig 85 provides another example obtained from a man of forty three who had a myocardial infarction in the anterior wall It shows sinus rhythm the R R intervals varying between 0 88 and 0 94 second (rate 63–68) There is evidence of myocardial damage (slight distortion of the R T segments sharp inversion of the T waves in leads 1 and 2) In lead 1 the second sinus beat is followed by a ventricular extrasystole with a coupling of 0 46 second the post extrasystolic interval is compensatory After the next sinus beat a ventricular extra systole with a coupling of 0 44 second occurred which in its turn was succeeded by an abnormal ventricular complex of which it could not be stated whether this was another ventricular extrasystole arising from a different focus or a return extrasystole with aberrant intra ventricular conduction The interval between the sinus beats preceding and succeeding these two abnormal ventricular complexes measured 1 76 seconds that is there was no disturbance in the dominant rhythm The absence of a P wave before the second abnormal complex is inconclusive since in auricular or return extrasystoles they are often very small or absent in lead 1 The nature of this unusual arrhythmia becomes clear from lead 2 The middle of this lead shows a sinus beat followed by a ventricular extra systole with compensatory post extrasystolic pause (coupling + post extrasystolic interval = 1 62 seconds cycle length of sinus rhythm 0 81 second) The next sinus beat is followed by a ventricular extrasystole with the same coupling (0 45 second) and having the same shape except for an inverted P wave being visible in its final deflection After a P R interval of 0 28 second this extrasystole was followed by a ventricular complex which differed in shape from that of the sinus beat though having the appearances of a supraventricular beat The interval between the two sinus beats preceding and succeeding these two abnormal complexes measured 1 80 second and there was thus a shift of the dominant rhythm The interval between the inverted P wave of the returning impulse and the P wave of the next sinus beat measured 0 96 second as compared with the calculated cycle length of 0 81 of the sinus



Fig 84 —Lead 2 Return extrasystoles precipitated by a ventricular extrasystole For further explanation see text

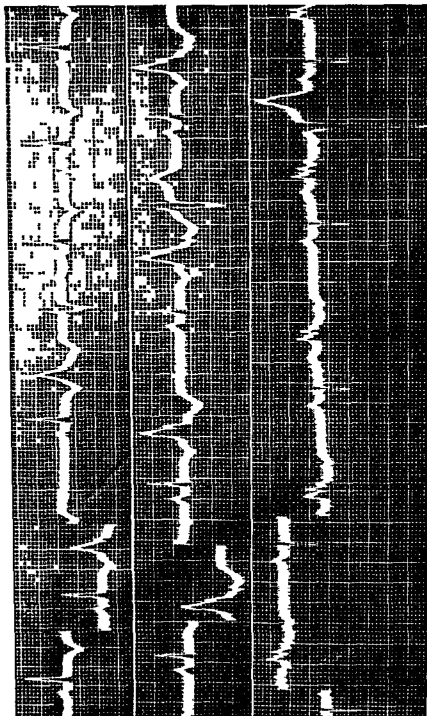


Fig 85—The three standard leads Return extrasystoles precipitated by ventricular extrasystoles The return extrasystoles show aberrant intra ventricular conduction and reached the sinus node

rhythm The most likely interpretation of this portion of the record is that the second abnormal ventricular complex was a return extrasystole with aberrant intra ventricular conduction which reached the sinus node and which was precipitated by the ventricular extrasystole The first sinus beat in lead 2 is also followed by a ventricular extrasystole with a coupling of 0 44 second It shows the same kind of inverted P wave in its final deflection as the third extrasystole but this is not followed by a ventricular complex and there is no shift of the sinus rhythm The inference is that this extrasystole too returned to activate the auricles but the impulse failed to reach either the sinus node or the ventricles return extrasystole with blocked ventricular conduction

The only other clinical observations of this phenomenon of which we are aware are those of Levin (1941) Schott (1951) and Kistin and Landowne

Levin s case is unique in that return extrasystoles were precipitated by both A V beats and ventricular extrasystoles with retrograde conduction to the auricles Apart from this his report is of interest in several other respects The patient gave a history of rheumatic fever at the age of twenty one and of an infection of the legs in the following year Several years later numerous electrocardiograms were taken during broncho pneumonia with pleurisy (Levin and Ochoa) which showed an unusual variety of arrhythmias namely sinus tachycardia auricular flutter A V rhythm with bundle branch block dissociation with interference and isorhythmic dissociation This was attributed to a toxic effect of the acute infection upon the conducting system previously damaged by rheumatic fever Subsequently (Levin 1940) reciprocal rhythm was found amongst various other arrhythmias including dissociation with interference Further studies of the reciprocal rhythm originating from the A V node showed the unusually long retrograde conduction times of 0 6–0 75 second the forward conduction times being 0 30–0 35 second The R P interval of the ventricular extrasystoles with retrograde conduction was shorter (0 5 second) than that of the A V beats which at first sight is surprising since the path of retrograde conduction of ventricular extrasystoles obviously is considerably longer than that of beats originating in the A V node Levin puts forward good reasons for attributing this phenomenon to facilitation (Bahnung)* of retrograde conduction of the ventricular extrasystoles by the preceding beat (whether of A V or S A origin) since the ventricular extrasystoles which gave rise to return beats followed the preceding beats at relatively shorter intervals than did those of A V origin (Skramlik 1920a *see* also p 126 Retrograde Conduction of Ventricular Extrasystoles) Another interesting observation in his case previously made by Cutts was that occasionally coupled beats of the same time sequence and shape in the electrocardiogram occurred as unquestionable return extrasystoles but without a P wave being visible between the two ventricular complexes forming the couple This is interpreted as indicating that return extrasystoles may be produced by an impulse originating in the A V node which activates the auricles and returns to the ventricles without giving rise to an auricular systole which therefore does not seem to be indispensable in the production of reciprocating rhythm It seems even possible that in such cases the impulse returns in or in the vicinity of the A V node without activating the auricles

The observation reported by Schott (1951) was made in a man of fifty two who during convalescence from acute glomerulonephritis developed an acute pyelonephritis which is a very unusual combination During that period an extrasystolic arrhythmia was recorded mostly presenting as trigeminal rhythm two ventricular extrasystoles following in succession On several occasions the second extrasystole of such groups was followed by a supra ventricular complex which could be shown to be a return extrasystole precipitated by the second extrasystole The time relations indicated that the impulse was conducted in a retrograde direction as far as the S A node with consequent shift of the dominant rhythm

* For definition of this term see p 136


Fig 86 —Lead 2 Most probably sino-auricular block with escaped beats simulating return extrasystoles but possibly return extrasystoles with alternation of pathway of activation of auricles Time base 0 2 second

In one instance a return extrasystole with blocked ventricular conduction had to be assumed In some respects this observation resembled that illustrated in Fig 85

The important recent paper by Kistin and Landowne which contains at least one instance of return extrasystoles precipitated by ventricular extrasystoles with retrograde conduction to the auricles is discussed in some detail in the section on Retrograde Conduction of Ventricular Extrasystoles (p 126)

While in cases of A V rhythm with supraventricular premature beats in which reciprocating rhythm is considered sharply inverted P waves in leads 2 and 3 form the rule the varying in shape of such P waves and even alternation in direction do not exclude such a possibility Decherd and Ruskin have published several instances of such an arrhythmia in which two retrograde P waves sometimes of varying shape were found with one A V beat the first indicating very rapid retrograde conduction and the second with a considerably longer R P interval giving rise to reciprocation This is considered by these authors as indicating a double auricular pathway resulting in two activations of the auricles by the same A V impulse the second of which gives rise to a return extrasystole

A personal observation seems to illustrate the possibility of such a variation in the direction of auricular activation in a case of return extrasystoles A series of five coupled beats is shown (Fig 86) the first of each couple being of A V origin Between the first and second beat of each couple a P wave is recorded which is alternately inverted and upright The inverted P waves follow the preceding QRS complexes with a R P interval of 0 48 second and in their turn are followed by a supraventricular complex with a P R interval of about 0 2 second (the first third and fifth couple) In the second and fourth couples on the other hand the P waves are upright the R P intervals being 0 4 and the P R intervals being 0 3 second respectively The most likely explanation of this tracing taken by itself would be return extrasystoles with alternation of the pathway of activation of the auricles This interpretation would be supported by the observation that the inverted P waves are constantly associated with longer R P and shorter P R intervals than the upright ones and that there is an inverse relation between the R P and P R intervals On some occasions only inverted P waves were recorded which also accords with this interpretation Many other tracings of this patient however which were published (Scherf and Shookhoff 1926b Fig 13 Wenckebach and Winterberg 1927 Figs 339 340 342 343) showed sino auricular block over long periods If in this arrhythmia automatic ventricular escape beats occur followed by sinus beats at varying intervals the P R intervals of the sinus beats are known to vary and to show also the inverse relationship between the R P and P R intervals The alternative explanation of the reproduced record offers itself therefore that it indicates sino auricular block with escape automatic ventricular beats The varying shapes of the P waves

would not in this case be against this diagnosis since this is a common occurrence in sino auricular block and even during regular sinus rhythm records of this patient showed continual changes in the shape and often inversion of the P waves due to aberrant intra auricular conduction This record illustrates that if taken by itself no objection could be raised against a diagnosis of return extrasystoles with alternation of the pathway of activation of the auricles whereas the alternative diagnosis of sino auricular block with ventricular escape is equally well founded when the other records of the same patient are given due consideration A decision between these two possibilities cannot be made with certainty and this instance provides an instructive example how fallacious the interpretation of short records of more complicated arrhythmias is likely to be

In addition to the cases discussed so far others have been reported in which we consider the diagnosis of return extrasystoles questionable Those published before the advent of electrocardiography cannot be accepted as established (Wenckebach Muskens) Other cases which we consider doubtful are Jones and White Wolferth and McMillan their statement that in their Case 2 a 2 1 block was present is not acceptable as stated on p 134 (retrograde conduction in A V block) and therefore their conclusion of a reciprocal beating auricle ventricle auricle is invalid Blumgart and Gargill (1930) Cases 2 3 and 4 Fogelson (the short indistinct records are inadequate for interpretation) Korth and Schrumpf (in Case 1 the diagnosis is certainly erroneous in Case 2 possibly correct but not proven) Bain (as far as ascertainable in the short reproduced record there was an independent auricular rhythm) Langendorf Katz and Simon (1944) whose case was in our opinion one of interpolated ventricular extrasystoles the varying shape of the P waves of some of the post extrasystolic beats being due to slight variations in the position of such waves in relation to the preceding T waves on which they were superimposed Mesquita (Case 3 more likely conducted beats during supernormal phase of A V beats Case 4 more likely interpolated ventricular extrasystoles Case 5 coronary sinus rhythm with Wenckebach periods) Bix (Case 2 blocked and conducted auricular extrasystoles whereby the post extrasystolic beats have P waves of the same abnormal shape as the extrasystoles)

Longer periods of reciprocal rhythm in clinical cases have been reported by Fischer and by Samojloff and Tschernoff In Fischer s case attacks of tachycardia occurred which were initiated by an A V extrasystole His interpretation of the records is that the extrasystole resulted in a delay of the activation of the ventricles by the subsequent supraventricular impulse and that for this reason the ventricular impulse was reversely conducted to the auricles which it reached outside their refractory period and in this way a reciprocating rhythm is supposed to have ensued The explanation is based on an assumed tendency of the ventricular contraction to spread to the auricles Paroxysmal A V tachycardia seems a far more likely explanation Samojloff and Tschernoff interpret some of their tracings as indicating the simultaneous presence of two reciprocating rhythms one originating from an A V beat and the other from an extrasystole with retrograde conduction The possibility of such an occurrence is admitted but cannot be considered proved In the case published by Naim as an instance of paroxysmal tachycardia due to reciprocal rhythm there is the alternative possibility that the arrhythmia was paroxysmal auricular tachycardia with blocking of some of the auricular extrasystoles A similar interpretation seems probable in the case of Codina Altes and Beristain and of Bix (Case 1) Altogether in the instances which have been reported of return extrasystoles precipitated by sinus beats we find that auricular extrasystoles and paroxysmal auricular tachycardia is an alternative and more likely explanation

In the differential diagnosis of cases of suspected return extrasystoles the main difficulty consists in distinguishing this arrhythmia from dissociation with interference or auricular parasystole As mentioned above the deciding factor is whether or not there is evidence of an independent rhythm activating the auricles As in so many arrhythmias only longer

records allow a diagnosis to be made with any degree of certainty Luten and Jensen stressed the importance of auricular parasystole in the differential diagnosis Zeisler pointed out that many cases considered to be examples of reciprocal rhythm actually were cases of dissociation with interference but seems to have gone too far in his rejection of the former diagnosis the reverse mistake is also not unlikely for an independent auricular pacemaker may be simulated in cases in which A V rhythm with a fairly constant R P interval and reciprocal beats is present (Decherd and Ruskin) A case interpreted as dissociation with interference and intra auricular disturbances of conduction simulating in parts reciprocal beats has been reported by Schott (1937) Both conditions were present in the same patient at different times in Levin s case (1941) discussed above

Physiological Considerations

Experimentally the re activation of auricles and ventricles by the same impulse was first described by Mines (1913) in the electric ray and frog after the application of rhythmic stimuli at some particular rate the cessation of the stimuli was followed by a quick recipro cating movement of the auricle and ventricle or of ventricle and bulbus The appearance of the heart gave the impression that the beats of the ventricle were caused by those of the auricle and bulbus while these in turn were caused by the ventricle This reciprocating rhythm could be stopped by a properly timed induction shock Subsequently Mines (1914) amplified these experiments on portions of auricle and ventricle of the tortoise rings cut out from auricles of elasmobranch fishes and of ventricles of large dogs and cats It will be noted that the clinical observations on return extrasystoles as well as the electrocardio graphic findings discussed earlier in this section differ from Mines result in that only one or at most two return extrasystoles were seen whereas in Mines experiments and those of Garrey both of which form the basis of the theory of circus movement such rhythms lasted for considerable periods In order for a reciprocating rhythm to be possible it has to be assumed that part of the tissue is in a refractory state at a time at which normally it would be excitable This results in a delay of conduction as well as in changes in the path of the excitation which owing to the presence of islets of refractory tissue pursues longer and more devious routes The excitation wave in travelling through muscle in this state will be delayed in journeying between given points since it will swerve from side to side as it passes through the only channels open to it The degree in which it swerves may be so great that it reaches muscle at a greater distance before it reaches by returning muscle lying at a shorter distance from its starting point (Lewis)

A return of the excitation wave as a result of the presence of refractory tissue which is implied in these words of Lewis was experimentally established by Schmitt and Erlanger on strips of ventricular muscle of the turtle their work also demonstrated that the return of the excitation wave depended on the presence of unidirectional block that is of the presence of tissue in such a high state of refractoriness that conduction in one direction failed In their experiments strips of ventricular muscle were mounted through five chambers which were divided by rubber curtains and conduction was depressed by electrical polarization cold and alteration in the ionic balance (KCl withdrawal of Ca) also locally by the pres sure of the dividing rubber curtains The degree of impairment of conduction proved to be unequal according to the direction in which the excitation was made to spread through the strip (called heterodromia) reaching the degree of unidirectional block in which a stimulus was blocked in one direction while being conducted in the opposite one (called mono dromia) In eleven experiments it was found that when heterodromia of such a degree that it bordered on monodromia was present the impulse after having traversed the strip in one direction returned to excite a second time that part of the strip from which it had originated This is explained by the assumption diagrammatically illustrated in Fig 87 that in the zone of depressed conduction only a fraction of the fibres conduct the impulse

and this at a reduced speed whereas the remaining fibres in which conduction is even more impaired fail to conduct altogether in the original direction impairment of conduction having reached the stage of unidirectional block (monodromia) After reaching normally excitable tissue beyond the zone of impairment the impulse turns back and passes through those fibres which not having conducted in the original direction are excitable and conduct the impulse in the opposite direction so that it subsequently reaches the excitable tissue again from which it originally started Schmitt and Erlanger applied these findings to explain certain varieties of extrasystoles They argued that if an area of depressed conductivity is assumed to be present in an ultimate twig of the conducting system there producing locally unidirectional block in the direction from conducting system to myocardium the excitation wave would enter the nearby myocardium from the penultimate twig only by

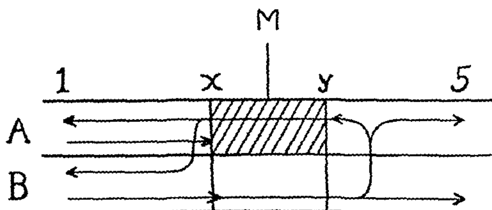


FIG 87—Diagram illustrating unidirectional block and return of impulse A and B two strata of fibres or two fibre paths passing through a curtain applied at M under which the fibres were subjected to pressure injury and KCl poisoning Segment x y area of greatly slowed conduction in both directions A being more affected than B in A monodromia (hatched area) An impulse precipitated at 1 starts with the same rate in A and B but is blocked in A at x proceeds at a reduced velocity in B returns beyond y and passes the area of monodromia in the direction 5 1 re activating A and B between x and 1 these portions having become excitable again From SCHMITT and ERLANGER (*Amer J Physiol*)

other branches but be conducted backwards through the affected twig If during that time the adjacent myocardium had become excitable again it could then produce a second contraction This conception seems to us incapable of explaining the great majority of extrasystoles for reasons which will be discussed in the appropriate chapter (pp 483–4) Their experiments are however of great importance for the understanding of return extra systoles Similar observations on reflected excitation waves travelling in a direction opposite to that of the original wave were made by Segers on isolated strips of the tortoise heart Such reflected waves could be obtained from areas modified by adrenaline calcium or barium Anodal polarization had a similar effect in the nerve of crabs (Arvanitaki)

There is no doubt that this particular variety of extrasystoles is due to a re entry mechanism Applying Schmitt and Erlanger s findings Scherf (1941) postulated a functional longitudinal dissociation of some of the auriculo ventricular conducting system whereas the part just above the bifurcation may be employed by both the A V beat and by the return extrasystole to which it gave rise (*see* Fig 88a) The numerous fibrinous septa between the strands of the specific system may facilitate such dissociation Decherd and Ruskin in

order to explain certain of their observations discussed above have modified this conception by assuming an area of refractory tissue of varying size and shape and/or varying stages of recovery situated at the junction of the atrial and ventricular portions of the A V node or perhaps near the junction of the nodal tissue and auricle (*see* Fig 88b and c) If an impulse spreading along pathway A encounters an area of relative refractoriness its conduction will be delayed Assuming further an area of greater refractoriness in area B blocking the spread of the impulse in this direction this and the adjacent area C will have been rendered completely refractory for a time by the blocked impulse and therefore will block the passage of an impulse in the direction to the ventricles If however the delay of conduction through area A is sufficiently great for some part of the adjacent area to have regained excitability at the time when the impulse has penetrated the area A the impulse will be capable of spreading through excitable tissue to the region below the A V node Owing to the delay of its spread in the retrograde direction through A and perhaps also of that in the orthograde direction through the partially recovered portion of area BCD (Fig 88b) this impulse will reach the ventricles outside their refractory period and thus produce

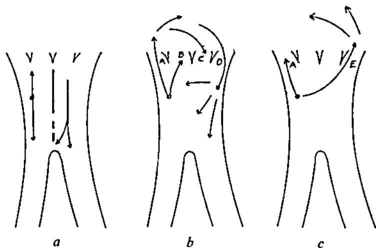


FIG 88 —Diagram illustrating various conceptions regarding the site of areas of dissociation or refractory tissue underlying the origin of return extra systoles From DECHERD and RUSKIN incorporating SCHERF 1941 *Tex Rep Biol Med*

the extrasystole This conception would also afford an understanding for the double auricular pathways variations in the size and shape of the area of refractoriness could allow rapid retrograde conduction of the impulse through one pathway say A (Fig 88b and c) with sufficient time for the auricle to respond to a second A V impulse being conducted with a considerable delay through another pathway say B or E this second impulse producing a second auricular contraction and subsequently re entering the infranodal tissue by forward conduction as in the previous example

These two views have the essential conception in common that they postulate an area of refractoriness in the vicinity of the A V node in the neighbourhood of which the impulse returns or sends back a subsidiary impulse to the ventricles Scherf s conception places it in a longitudinal direction through the node itself whereas Decherd and Ruskin think of it as a more extensive area varying in shape and size situated more towards the auricle The exact localization of the area of dissociation or refractoriness probably varies in different cases Decherd and Ruskin emphasize that in the majority of cases the returning impulse

discharges the nodal pacemaker and from this as well as from several other features of their records conclude that the same tissue is affected by the impulses going in the two directions The inverse relationship between the P R and R P intervals of the return extrasystoles strongly suggests that at least for part of their path the two impulses employ the same channels That this is not the explanation of all the cases is proved by the observation that return extrasystoles may be interpolated (*see* Fig 82) and Decherd and Ruskin concede that for at least these cases some kind of dissociation or protective block of the A V pacemaker has to be postulated In the absence so far of histological reports of cases known to have shown return extrasystoles these views are necessarily speculative but it should be recalled that Ashman and Hafkesbring s experiments on asymmetrical compression have demonstrated the importance of the shape of damaged tissue in the production of unidirectional block (*see* p 134) and the very few histological reports on cases having shown retrograde conduction in complete A V block seem to emphasize the importance of the site of the lesion Only when histological findings in cases of return extrasystoles become available will it be possible to pronounce a more definite judgment about the nature site and boundaries of the lesion giving rise to this rare arrhythmia The salient fact at this stage of our knowledge is that it constitutes a variety of extrasystoles which are unquestionably due to a re entry mechanism

In view of the small number of observations nothing can be said about any special clinical significance of return extrasystoles However perusal of the literature shows that a great proportion of such patients were suffering from pronounced structural heart disease (and were under the influence of drugs) Considering that in the vast majority the underlying rhythm was A V nodal rhythm this observation accords well with that of Ruskin McKinley and Decherd (1945) that amongst forty five patients showing A V nodal rhythm no fewer than 80 per cent had demonstrable heart disease The further findings of these authors that A V rhythm occurred in only 0 45 per cent of ten thousand patients of their Heart Station and that amongst their forty five patients with A V rhythm only three showed the variety with preceding activation of the ventricles which alone gives rise to return extrasystoles bring out an important reason for the great rarity of this arrhythmia

SUMMARY

If in experimental work A V rhythm is produced and auricular or ventricular extrasystoles are elicited certain alterations in the time sequence between auricular and ventricular systole occur temporarily in the first few post extrasystolic beats Such changes were observed only in certain analysable conditions and it could be shown that they were due to disturbances of conduction in the main bundle of His which did not affect either the A V node or the myocardium As in A V rhythm the impulses activating auricles and ventricles respectively travel in opposite directions relatively small changes in the speed of conduction in either direction result in comparatively large alterations in the time sequence between auricular and ventricular activation for this reason A V rhythm lends itself particularly well to investigations of this kind The importance of these findings in connexion with fundamental properties of cardiac physiology and pathology is discussed Clinically this phenomenon was observed with certainty in only one case

If during A V rhythm with preceding activation of the ventricles the activation of the auricles is delayed beyond a certain measure a return extrasystole may result by the return of the excitation wave in or close to the A V node towards the ventricles the same impulse thus activating the ventricles a second time The degree of delay in the activation of the auricles necessary for this phenomenon to occur varies in different experimental and clinical conditions In a similar manner return extrasystoles may also be precipitated by a ventricular extrasystole with retrograde conduction to the auricles Various methods of

producing return extrasystoles experimentally are described The literature on clinical observations showing this phenomenon is critically reviewed, and the differential diagnosis is discussed with special reference to distinguishing this arrhythmia from dissociation with interference and from auricular parasystole Hitherto unpublished examples of two successive return extrasystoles of return extrasystoles precipitated by ventricular extrasystoles with retrograde conduction to the auricles and of return extrasystoles possibly illustrating varying paths of auricular activation are reported The occurrence in man of a persistent reciprocating rhythm entailing more than two successive return extrasystoles cannot be considered as established

In order for a reciprocating rhythm to be possible a unidirectional block has to be postulated resulting from the presence in or near the A V node of refractory tissue which is responsible for the delay in and the abnormal direction of the spread of impulse As the salient point it is emphasized that reciprocating rhythm (return extrasystoles) can be considered as unquestionably being due to a re entry mechanism but that this mechanism is not acceptable as an explanation for all or even the majority of extrasystoles

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RETROGRADE CONDUCTION OF VENTRICULAR EXTRASYSTOLES TO THE AURICLES

It would be surprising if as believed until recently in man ventricular extrasystoles were only rarely conducted to the auricles since both in muscle and nerve impulses are known to travel in both directions and in many animals the conduction of impulses from one part of the heart to another is by no means confined to one direction

Experimental Observations

In the heart of Ascidiae the sequence of contractions of the various portions normally reverses its direction periodically (Gaskell 1883) the heart of certain fish shows a disposition to reverse the order of contraction (ref *see* Skramlik 1927a) and by a single mechanical stimulus applied to the *conus arteriosus* of the heart of the skate the normal sequence of contraction can be reversed for several minutes while the normal order can just as easily be restored by a gentle stimulation of the sinus end (Gaskell 1883) In the heart of certain species of fish retrograde conduction takes place faster and with greater ease (also persists longer in the dying heart) than orthograde one (Carlson v Skramlik 1924 1927a 1930) though recently Kisch (1948) has cast doubt upon whether this holds good as a general rule in electrographic investigations he found that the A V conduction was slower than the V A one in only two out of nineteen experiments and that the relations between the speeds of retrograde and orthograde conduction depended on the site at which the extrasystole was produced

Concerning the amphibian heart reversal of the normal order of contraction in the frog s heart was first reported in 1850 by Hoffa and Ludwig after application of tinct opii to the septum stimulation of the ventricle produced ventricular contraction followed by that of the auricles and bulbus

Engelmann (1895 1896) pointed out that conduction in only one direction depended *inter alia* on the speed of change of those physiological conditions which acted as the stimulus and that in the frog s heart three different kinds of fibres were involved (atrial connecting fibres and ventricular) which differed in the speed of their contractions and conduction

If during the passing of the impulse from one category of fibres to another the impulse meets fibres which by virtue of their inadequate speed of conduction do not respond to the oncoming stimulus its conduction is blocked and since the connecting fibres have the lowest rate of conduction it is here that the propagation of the impulse ceases for this reason Engelmann termed the connecting fibres Blockfasern (blocking fibres) By differences in temperature or the application of poisons (veratrine) he was able so to alter conduction in the frog s sartorius (where normally it is equal in both directions) that conduction in one direction was abolished whereas that in the reverse remained intact thus imitating to a certain extent the conditions found in the heart From these experiments Engelmann drew far reaching conclusions about the myogenous nature of the propagation of the cardiac impulse the validity of which was later queried by Skramlik (1920b)

Skramlik who carried out extensive investigations on the retro and orthograde conduction in the frog s heart found that unless special circumstances are present conduction between two parts of the heart is unequal and faster in the normal (sinus auricles auricles ventricle ventricle bulbus) than in the reverse direction To a certain extent this is probable even in the ventricle where apex base would be the normal direction By various means it is possible not only to abolish retrograde conduction but also to block exclusively the orthograde one conduction only in the normal direction was preserved if all connexions between auricles and ventricle were severed except a narrow dorsal bundle or if the ventral communications were damaged by heat while the dorsal portions were protected by cooling On the other hand if the septum alone was left intact only the retrograde conduction remained Skramlik concluded that the septum mediates the retrograde conduction whereas certain dorsal bundles effect exclusively or predominantly orthograde conduction the ventral and lateral bundles are concerned with both (Skramlik 1920b)

If as is the rule during cardiac standstill after application of Stannius first ligature retrograde conduction is absent it can be initiated by stimulating the auricles thereby producing contractions in the normal sequence Once retrograde conduction is established in this way it persists so that successive ventricular stimuli are conducted to the auricles but if stimulation is interrupted retrograde conduction no longer takes place when stimulation of the ventricle is subsequently resumed The longer the standstill of the heart the more numerous the orthograde stimuli have to be in order to facilitate retrograde conduction Similar conditions were observed on the junction between ventricle and bulbus (Skramlik 1920a and b) These observations which demonstrate facilitation* of retrograde conduction by stimuli passing in the normal direction were discussed at some length since they also afford an understanding for the retrograde conduction of idioventricular impulses in cases of complete A V block (*see* p 133) The reverse phenomenon namely facilitation of orthograde conduction by retrograde stimulation of auricle from ventricle when orthograde conduction had ceased was found in the fish heart (Skramlik 1927b)

The separation between conduction in the two directions is much less marked in the heart of the tortoise (Ishihama)

In the mammalian heart retrograde conduction to the auricles was reported by Mc William in 1888 and by Bayliss and Starling in 1892 In the dog Stassen demonstrated reversed conduction from the ventricle to the auricle during vagus stimulation In most animals it was found to take place less readily than the orthograde one the V A intervals exceeding the A V ones of normal conduction but that reverse conduction over a certain distance at least as far as the A V node is the rule is now generally accepted (Scherf and Shookhoff) If retrograde conduction is produced in the dog alternation of the ventriculo auricular conduction times is not uncommon (*see* Fig 80)

The importance of facilitation is illustrated by the observation that if a ventricular rhythm is produced in dogs by means of induction shocks the auricles respond to the ventricular beats only after a variable number of cycles (from three to twenty seven usually from five to twelve) (Lewis and Oppenheimer) Hukuhara and Komita on the other hand failed to find retrograde (V A) conduction of ventricular extrasystoles in the dog

Absence of retrograde activation in mammals in particular in man does not necessarily mean that conduction in the reverse direction is blocked The time relations are such that in most cases the retrograde impulse will reach the auricles and even more certainly the S A node at a moment when they are already being activated by the next sino auricular impulse and therefore are in their refractory stage This is due to several factors the most important ones being the heart rate the delay of conduction in the A V node (Hering Lewis 1921) and the length of the refractory period of the auricles

For definition of this term see p 136

Clinical Observations

Since mechanical records alone do not allow a differentiation between ventricular extra systoles with retrograde conduction to the auricles and A V extrasystoles the earlier reports of cases of the former arrhythmia published before the advent of electrocardiography (Pan Volhard Gallavardin) cannot unreservedly be accepted The same holds good for the case published by Tancre though it is often quoted as the reproduced tracings are in adequate

The first convincing clinical example of ventricular extrasystoles with retrograde conduc tion to the auricles is the case published by Hart in 1912 in which an abnormally shaped P wave on the downstroke of the initial deflections of ventricular extrasystoles indicated retrograde conduction This interpretation was supported by the observation that if such extrasystoles occurred in groups only alternate extrasystoles showed the above sign of retrograde conduction A similar instance seems to be Case 4 in the series of Robinson and Herrmann (1921) though the authors do not mention retrograde conduction Other cases in which the presence of this arrhythmia in man seems established are those of Scott (1922) (electrocardiogram and venous pulse tracings) Gussenbauer (1923) whose case is *particularly convincing since in the same record interpolated extrasystoles of the same shape* without retrograde conduction were available for comparison the post extrasystolic inter vals were compensatory so that it has to be assumed that the retrograde impulses did not reach the sino auricular node Potts and Ashman (1926), in a case of dextrocardia Allan (1926) in a case of ventricular paroxysmal tachycardia with retrograde conduction of every second beat also showing the importance of facilitation Samet in whose case the post extrasystolic interval was not compensatory but the interval between the inverted P wave of the extrasystole with retrograde conduction and the following P wave was slightly (0 06 second) longer than the normal P P intervals which indicates that the retrograde impulse was conducted as far as the sino auricular node Similar conditions are shown in a tracing of Lewis (1925) though Lewis concedes an alternative explanation of this record Dressler on the ground of his observations in two cases emphasized the importance of facilitation of conduction for the establishment of retrograde conduction In his first case the presence of retrograde conduction of ventricular extrasystoles could be demonstrated particularly clearly since the underlying rhythm at times was dissociation with interference (*see* p 178) at other times A V rhythm with preceding activation of the ventricles and the inverted P waves following the initial deflections of the ventricular extrasystoles had the same shape in the electrocardiogram as the P waves during A V rhythm During the periods of fully developed A V rhythm retrograde conduction of ventricular extrasystoles occurred almost without exception this observation illustrating the importance of facilitation Occasionally however ventricular extrasystoles were conducted to the auricles when the underlying rhythm was dissociation with interference Since in this arrhythmia a block of the con duction of A V impulses to the auricles has to be postulated (*see* p 179) the retrograde conduction of ventricular extrasystoles to the auricles is difficult to understand As in this case the transition from A V rhythm to dissociation with interference was associated with a conspicuous slowing of both the independent auricular and ventricular rhythms considered *to be due to a vagal effect Dressler explains the retrograde conduction of ventricular extra* systoles during dissociation with interference by the assumption that the increase in vagal tone resulted in a diminution of strength of the A V impulses which for this reason were no longer conducted to the auricles whereas the strength of the impulses of the ventricular extrasystoles was less if at all diminished

Ventricular extrasystoles with retrograde conduction in which the impulse reached the sinus node were also described by Meyer

In order for a diagnosis of retrograde conduction of ventricular extrasystoles to the

auricles to be made from the standard leads it is necessary that in the electrocardiogram a P wave, which is low positive or isoelectric in lead 1 and sharply inverted in leads 2 and 3 follows an abnormal QRS complex itself not preceded by a P wave with a R P segment equal to or exceeding the P R interval of the individual case the whole of such P waves usually designated P has to be below the line otherwise occupied by the S T segment Caution is necessary not to confuse with such P waves normal P waves occasionally visible in the final deflection of the extrasystole The post extrasystolic intervals may be shorter than compensatory or compensatory according to whether or not the retrograde impulse reached the sino auricular node The diagnosis of this arrhythmia is rendered more certain if only some of the extrasystoles are conducted in the reverse direction so that the shape in the electrocardiogram of undistorted extrasystoles is available for comparison and if the post extrasystolic interval is not compensatory Even so the differentiation from A V extra systoles with preceding activation of and aberrant conduction in the ventricles may be difficult if not impossible In the latter arrhythmia there would be the same shape and position in relation to the QRS complexes of the P waves as well as abnormally shaped ventricular deflections but since ventricular extrasystoles tend to have the same shape in the electrocardiogram whereas with aberrant conduction in the ventricles of supraventri cular impulses the degree of aberration tends to vary from beat to beat identical forms of the abnormally shaped ventricular complexes would favour the diagnosis of ventricular extrasystoles with retrograde conduction

The value of oesophageal leads for the detection of retrograde P waves in this arrhythmia was emphasized by Brown

Quite recently Kistin and Landowne published an important paper in which employing oesophageal leads they reported evidence of retrograde conduction of ventricular premature beats in fifteen out of thirty three unselected subjects These authors found (unipolar) oesophageal leads from atrial levels (37 5 cm) particularly informative The characteristics of the P waves interpreted as indicating retrograde conduction are listed as follows (1) they may differ in shape from the sinus P waves (2) they may be premature in relation to the sequence of the sinus P waves and in such event the P P interval—that is the interval between the retrograde P and the following sinus P wave—is longer than the P P one and the interval between the last P wave before and the first P wave after the extrasystole may be compensatory or shorter than compensatory (3) such P waves occur only within a limited range of time after the preceding extrasystolic QRS complex A further reliable criterion of retrograde conduction were fusion P waves intermediate in shape between P and P waves These authors demonstrated in our opinion conclusively that such oeso phageal leads did indicate retrograde conduction in a considerable proportion of cases in which the simultaneously recorded lead 2 failed to do so They put forward good reasons to explain this based on the effect upon the P waves in the oesophageal lead and lead 2 respectively of two such excitation waves travelling between the S A and A V nodes in opposite directions These authors also point out that in quite a number of instances a compensatory post extrasystolic interval may be a fortuitous occurrence caused by the unavoidable inclusion in the measurement of this interval of variations in the sinus rate and margins of error of measurements On the other hand post extrasystolic intervals after ventricular extrasystoles with retrograde conduction tend to be truly compensatory since the retrograde impulse is likely to reach the sinus node only after the initiation of the next S A impulse This follows from the fact that such retrograde conduction takes place with less prematurity than does the occurrence of some auricular extrasystoles the post extrasystolic intervals of which tend to be shorter than compensatory Other noteworthy findings of these authors were that the ventriculo auricular conduction time in the human heart is not consistently greater than the orthograde atrio ventricular one and that in two of their cases the intervals of retrograde activation fell into two discontinuous groups which

is interpreted as denoting two pathways of retrograde conduction (An analogous assumption regarding a double pathway of auricular activation in certain instances of return extra systoles was made by Decherd and Ruskin *see* p 118) In one of these authors cases an otherwise healthy subject with short runs of ventricular tachycardia the first ectopic beat of such series did not show evidence of retrograde conduction whereas this occurred in the remaining beats of such series This is the clinical counterpart of Lewis and Oppenheimer s experimental observations discussed earlier in this section and illustrates the importance of facilitation

In our opinion the tracings published by Kistin and Landowne are convincing and these findings may necessitate a reconsideration of our views about the incidence of retrograde conduction of ventricular extrasystoles in the human heart In view of the great physiological importance of the points raised by this publication we should like to reserve our final judgment until these findings are confirmed and corroborated by other leads further information could be expected for instance from unipolar limb or certain intracavity leads

A few personal observations may now be described

Fig 89 provides an example which also demonstrates the value of the chest leads It was obtained from a seventy year old patient with syphilitic aortitis atheromatosis and angina of effort One ventricular extrasystole is reproduced in leads 1 and 3 respectively which at first glance give the impression of being of the usual variety Closer inspection and measurement show however that the post extrasystolic intervals are far shorter than compensatory that no P wave is visible at the expected time after the extrasystole and that a small wave was inscribed in the descending limb of the T wave of the extrasystole in lead 1 and the ascending limb of the S wave in lead 3 the interval between such waves and the following P waves equalling the normal P P intervals This suggests ventricular extra systoles with retrograde conduction and this assumption is made more probable by the features of lead CR 3 in which three ventricular extrasystoles were recorded the first two of which show well defined inverted P waves on the ascending limb of the S waves the R P intervals being 0 15 and 0 16 second as compared with the 0 15 second of the P R intervals of the sinus beats The R R intervals being 1 09–1 13 seconds and the coupling of the first two extrasystoles being 0 45 second the post extrasystolic intervals of 1 44 and 1 40 seconds respectively fall far short of being compensatory and the P P intervals equal the P P ones The third extrasystole occurred with a longer coupling 0 52 second No P wave is visible on the ascending limb of its S wave and while it is therefore not possible to determine the R P interval the steeper ascent of the S wave and the greater height of the T wave as well as measurement backwards from the following P wave make it possible to state that its R P interval was shorter than the one of the two preceding extrasystoles This would have to be expected in view of the longer coupling The post extrasystolic cycle was terminated by an escape beat These observations point to an interpretation of ventricular extra systoles with retrograde conduction and the constancy of the shape in the electro cardiogram of the extrasystoles supports this view and allows to exclude the only other alternative namely A V extrasystoles with aberrant ventricular conduction The tracing also shows an interesting alteration in the shape of the P wave of the post extrasystolic beats following the second and third extrasystole such waves being more peaked than the other P waves This is reminiscent of similar conditions after auricular extrasystoles indicating that impulse formation continues in another auricular centre That such ectopic auricular impulse formation may continue for several beats after an auricular extrasystole was shown in Fig 46 Strong support of the presence of retrograde conduction is afforded by lead CR-4 in which the P wave is particularly distinct the P P interval equalling the P P one this portion of the record could hardly be interpreted in any other way

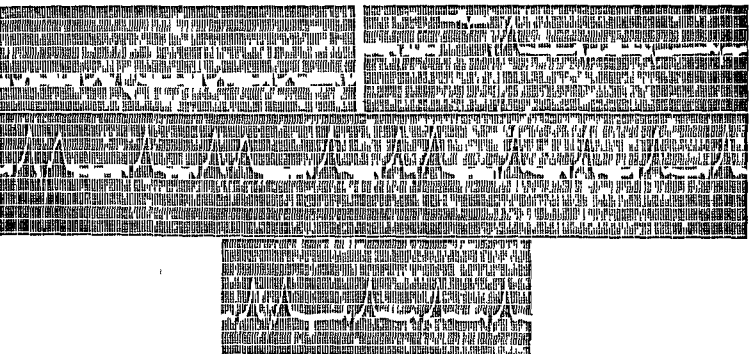


Fig 89 —Leads 1 3 CR 3 and CR 4 Retrograde conduction of ventricular extrasystoles For further explanation see text

Fig 90a was obtained from a sixty five year old patient with coronary sclerosis The tracing shows two sinus beats followed by a ventricular extrasystole in the final deflection of which an inverted wave is visible which has all the appearances of an inverted P (P) wave The R P interval measures 0 20 second as compared with the 0 13 second of the P R intervals of the sinus beats The post extrasystolic interval was fully compensatory *but since the P wave indicating retrograde conduction occurred at a time when the next* normal P wave was due this record is best interpreted as showing a ventricular extra systole with retrograde conduction reaching the auricles at the moment when the next normal impulse is being formed

Fig 90b obtained from a healthy man of forty six shows similar conditions After a sinus beat a ventricular extrasystole was recorded in the final deflection of which a P wave is visible occurring after a R P interval of 0 20 second at a time when the next



Fig 90 —Both tracings lead 2 obtained from different patients Retrograde conduction of ventricular extrasystoles

normal P wave was due The P R intervals of the sinus beats measured 0 18 second The post extrasystolic interval was more than compensatory and the P P interval (1 12 seconds) was longer than the normal P P ones (0 96–1 00 second) These time relations seem best explained by the assumption that the retrograde impulse reached the sinoauricular node there causing an inhibition of the formation of the subsequent impulse this phenomenon would be analogous to the one discussed in relation with the post extrasystolic intervals following auricular extrasystoles (*see* p 47) A case similar in many respects was pub lished by Holzmann

Regarding retrograde conduction of ectopic beats in parasystole, see chapter on Pararrhythmias , p 156

SUMMARY

Retrograde conduction of ventricular extrasystoles is common in certain animals but its occurrence in man has until quite recently been considered very rare In order for a diagnosis of this arrhythmia to be made *from the standard leads it is necessary that in the* electrocardiogram a P wave which is low positive or isoelectric in lead 1 and inverted in leads 2 and 3 follows an abnormal QRS complex itself not preceded by a P wave with an R P interval equal to or exceeding the P R interval of the individual case in leads 2 and 3

the whole of such P waves has to be below the line otherwise occupied by the S T segment The post extrasystolic interval may be shorter than compensatory or compensatory according to whether or not the retrograde impulse reached the sino auricular node The differentiation from A V extrasystoles with preceding activation of and aberrant conduc tion in the ventricles may be difficult if not impossible identical forms of the abnormally shaped ventricular complexes favour the diagnosis of ventricular extrasystoles with retro grade conduction Mechanical records do not make a differential diagnosis between these two arrhythmias possible and cases published before the advent of electrocardiography as indicating retrograde conduction of ventricular extrasystoles cannot unreservedly be accepted particularly since the alternative arrhythmia namely A V extrasystoles cannot be differentiated from such records A brief review of the published cases is given to which a description of three personal cases is added The importance of facilitation of conduction for establishing retrograde conduction is emphasized

If a recent observation based on oesophageal leads of the common occurrence of retro grade conduction of ventricular extrasystoles in the human heart is confirmed on larger series of cases our views about the incidence of this phenomenon will have to be recon sidered (For references see next section)

RETROGRADE V A CONDUCTION OF VENTRICULAR AUTOMATIC BEATS AND OF VENTRI CULAR EXTRASYSTOLES IN COMPLETE A V BLOCK

If as discussed in the preceding section the retrograde conduction of ventricular extra systoles was until recently believed to be a rare event in cases of sino auricular rhythm that of automatic ventricular beats and of ventricular extrasystoles in complete A V block was for a long time considered to be an impossibility That in the absence of conduction in the normal direction retrograde conduction should occur at all seemed so unlikely that all kinds of other explanations were put forward when clinical cases first came under observation in which this occurrence was seemingly present Yet in our opinion this phenomenon is not at all uncommon

Cohn and Fraser who were the first to report in 1914 a case of complete A V block in which some of the ventricular beats seemed to activate the auricles attributed the premature auricular contractions to a mechanical stimulation of the auricles by the contracting ventri cles the long refractory period of the auricles playing an important part Barker thought that the abnormal impulse responsible for auricular contraction being due to mechanical stimulation by the ventricles originated above the lesion in or near the A V node whence it was conducted to the auricles he specifically rejected the assumption of retrograde con duction Similar views were expressed by Wilson and Robinson

The first to suggest retrograde conduction of automatic beats in a case of complete A V block were Danielopolu and Danulescu (1922) Similar cases were reported (Veil and Codina Altes Wolferth and McMillan Froment *et al* Bain Kisch and Zucker a o) and by 1944 twenty five cases showing this phenomenon were collected in a critical review by Winternitz and Langendorf including six new cases More recent observations are con tained in the papers by Duclos (one case) by Segers (three cases in Case 3 retrograde im pulse precipitated a more rapid ectopic auricular rhythm with the same inverted P waves t rminated by an idioventricular beat which was also reversedly conducted) and by Galla vardin Froment and Balestier Their observation made in a forty eight year old woman with rheumatic mitral valvular disease and complete A V block showed that retrograde conduction took place only with idioventricular beats which had a P R interval varying between 0 43 and 0 52 second whereas with some beats occurring with a P R interval exceeding 0 52 second no retrograde conduction occurred This observation is interpreted

as probably indicating a supernormal phase of retrograde conduction Carotid sinus pressure slowed the auricular rhythm the P P intervals lengthening from 0 62 to 0 80 second and resulted in a conspicuous increase in the number of beats with retrograde conduction Atropine on the other hand (1 mgm given intravenously) accelerated the auricular rhythm and abolished retrograde conduction

While the reader is referred to the exhaustive paper of Winternitz and Langendorf which includes a complete list of such cases up to 1944 and a well reasoned rejection of all explanations other than retrograde conduction of automatic ventricular beats we propose to add a short description of two observations of our own and to discuss briefly some points which we consider to be of especial interest

Fig 91 was obtained from a seventy four year old man with hypertension and coronary sclerosis The record shows complete A V block (auricular rate about 65 ventricular 36) Inverted P waves (P) are seen after the third ventricular complex in lead 2 and after the first and fifth ones in lead 3 the R P interval being 0 18 second

This case shows some features which were observed in most of the records published so far the P waves indicative of retrograde conduction were inverted in leads 2 and 3 evidence of retrograde conduction occurred only when an automatic beat fell comparatively late in auricular diastole (the P R intervals preceding the beat with retrograde conduction being 0 6 0 66 and 0 74 second respectively) the R P intervals were well within the limits of normal forward conduction time the auricular rate was not fast the record was obtained from an old patient with evidence of structural heart disease

The P waves in any individual lead may vary somewhat in shape (*see* Fig 91 lead 3) this is due to the time of their occurrence within the R T (S T) interval and to interference between the retrograde P with the orthograde P if this is due at about the same time The latter mechanism constitutes one of the varieties of summation beats (For a recent general review of such beats (also called fusion beats) *see* Malinow and Langendorf)

Fig 92 reproduces an unusual record obtained from a sixty five year old woman suffering from anginal pain dizziness and attacks of fainting The tracing shows complete A V block The first third and fourth automatic idioventricular beats and the ventricular extrasystole are reversedly conducted to the auricles the initial ventricular deflections of these beats are followed by the characteristic sharply inverted P waves

The fact that retrograde transmission in the absence of conduction in the normal direction has to be accepted should be stressed since as late as 1931 its occurrence was doubted (Zeisler) Conclusive proof is contained in the paper by Wolferth and McMillan who showed that if a ventricular extrasystole with retrograde conduction follows an automatic beat with a fixed coupling the R P interval of the extrasystole is longer when the preceding automatic beat also was reversedly conducted Moreover in all published records retrograde conduction was only reported of beats occurring late in auricular diastole Neither of these observations could be explained by the assumption of a mechanical stimulation of the auricles by the ventricles nor would the time relations be compatible with Barker s view of the precipitation of an auricular extrasystole by the automatic beat In a *large proportion of the reported cases the block was unstable but retrograde conduction* was seen only when A V block was complete in the only case in which this occurrence was reported during 2 1 block (Wolferth and McMillan Case 2) in our opinion complete A V block actually was present since there was considerable variation in the length of the P R intervals

Retrograde conduction in the absence of orthograde one is a manifestation of unidirectional block the presence of which has to be postulated also in cases of dissociation with interference (*see* p 178) and return extrasystoles (*see* p 120) Such unidirectional block was produced in strips of ventricular muscle of the tortoise by asymmetric mechanical compression (Ashman and Hafkesbring 1929) These authors showed that if in this way a zone

Fig 91 —The three standard leads Retrograde conduction of automatic idioventricular beats in a case of complete A V block



Fig 92 —Lead 3 Retrograde conduction of automatic idioventricular beats and of a ventricular extrasystole in a case of complete A V block

of strongly compressed muscle is produced adjacent to one which is lightly compressed a stimulus produced at one end of the strip which first traverses the zone of strong compression was conducted to the other uncompressed end of the strip whereas a stimulus of equal strength precipitated at the opposite end and having to pass first through the lightly compressed area was blocked Moreover before irreciprocal conduction is thus produced the impulse will usually traverse the strip more rapidly in the direction from stronger to weaker compression than in the opposite one The explanation put forward is that in the more strongly compressed area the impulse is conducted with a larger decrement (*see also* Drury), the remaining strength is adequate for the stimulus to pass through the zone of less resistance With an impulse set up at the opposite end the decrement it suffers while traversing the lightly compressed area weakens it to such an extent that it fails subsequently to pass the strongly compressed part The same view had been put forward by Wolferth and Mc Millan with this apposite simile The point may perhaps be made clearer by the analogy to a runner who might be able to jump a broad stream at the beginning of his race and then overcome relatively minor obstacles whereas if the minor obstacles had come first he might have been so fatigued as to be unable to jump the broad stream

Dissociation with interference has already been mentioned as another condition in which unidirectional block is a prerequisite As a section is devoted to this arrhythmia this only need be said about it here that in it a faster A V rhythm and a slower S A rhythm co exist and that the slower S A rhythm at times interferes by conducted beats with the faster A V rhythm Such a condition is only possible if the centre of the slower rhythm is protected from the faster impulses originating in the A V node and this block can be effective only in the retrograde direction from the A V node towards the S A node whereas the spread of the excitation wave in the normal direction is unimpaired Retrograde conduction of automatic ventricular beats and of ventricular extrasystoles in complete A V block is *therefore the reverse of dissociation with interference and in accordance with Winternitz and* Langendorf could be termed dissociation with interference between ventricle and auricle

An attempt was made by Kline Conn and Rosenbaum to explain retrograde conduction in complete A V block by the supernormal phase of recovery According to Adrian and Keith Lucas who first described this phenomenon it can be defined as a temporary overswing of the recovery curve of excitable tissue after the transmission of an impulse during this period stimuli of an intensity which at any other time would be subliminal will become effective Its presence in cardiac muscle under definite experimental conditions was established by Adrian and several clinical cases have been reported (Scherf and Schott for a recent critical review *see* Mack Langendorf and Katz also chapter on Mechanism p 497) Its presence was made probable in Case 2 of Kline *et al* though the fact that in the short reproduced strip the P waves considered to have been due to retrograde conduction have the same shape in the oesophageal lead as the P waves of beats of sino auricular origin raises doubts about the criteria applied by these authors to determine retrograde conduction Even if the presence of a supernormal phase of recovery of conductivity is conceded as a possible explanation in this case it is inapplicable to others (Winternitz and Langendorf Case 2)

In the present state of our knowledge it seems to us preferable to consider facilitation of retrograde conduction by an orthograde impulse as the mechanism usually operative (*see also* Skramlik, p 127) This would account for the observation that in the majority of such cases retrograde conduction is observed only if the idioventricular beat showing this phenomenon occurs late in auricular diastole at a time when the next sino auricular impulse either has started or is about due The term facilitation is used here as commonly employed in neurophysiology in the wider sense of the German Bahnung It means in a general way that because of some antecedent or concomitant event the job is more easily done or a bigger job can be done (Lloyd) While the supernormal phase is of great importance

in facilitation thus defined other factors are likely to be also responsible for it This is more fully discussed in the chapter on Mechanism p 497 The relevant physiological observations providing a basis for considering facilitation as the underlying mechanism for retrograde conduction were discussed in the preceding section

According to Danielopolu and Danulescu the retrograde conduction of only those automatic beats which occur late in auricular diastole was due to the length of the refractory period of the auricles the duration of which could thus become measurable It was shown however by Winternitz and Langendorf that it is the state of the junctional region of depression or block and not of the auricle which determines whether retrograde transmission will occur or fail In one of their cases of complete block with occasional retrograde conduction at times an ectopic auricular rhythm was present characterized by inverted P waves (—P) at other times normal upright P waves were recorded (+P) (*see* Fig 93) Ventricular extrasystoles (P B Fig 93c) with retrograde conduction were also occasionally present The authors found that the earliest retrograde conduction after an

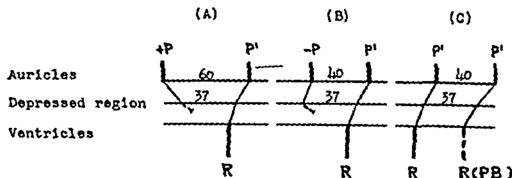


FIG 93 —From WINTERNITZ and LANGENDORF *Am Heart J*
For explanation see text

upright P wave occurred with a much longer +P—P interval than the earliest retrograde conduction after an inverted P (—P—P) Beats giving rise to a +P arise in or near the sino-auricular node whereas those producing —P are due either to a retrograde transmission or to a supra ventricular escape of a beat originating above the area of block The authors point out that in the longer +P—P intervals the additional time required by the impulse from above to reach the depressed region and by the ventricular impulse to travel from the depressed region to the auricle is included These time relations can be explained by the assumption that they are determined by the state of the area of depression but not by the length of the refractory period of the auricles

These observations have also a bearing on the question whether the retrograde transmission uses a path different from that of the orthograde one While the importance of accessory pathways is now definitely established in some instances (for example the Wolff Parkinson White syndrome) it seems probable that in the retrograde conduction of automatic ventricular beats and ventricular extrasystoles in complete A V block the same pathways are used at least for a distance This view is based on the findings of Winternitz and Langendorf also on the findings of Wolferth and McMillan mentioned earlier that the R P interval of a ventricular extrasystole is greater if the preceding automatic beat also shows retrograde transmission than when it does not A similar problem arises in connexion with return extrasystoles (*see* p 123)

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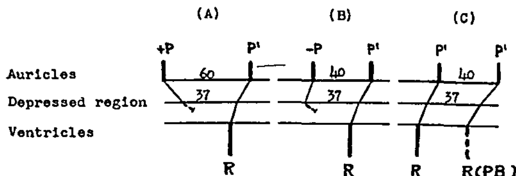


FIG 93 —From WINTERNITZ and LANGENDORF *Am Heart J*
For explanation see text

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As far as the scanty anatomical observations make it possible to express an opinion it seems that the site of the area of depressed conduction or block rather than the presence of accessory pathways is responsible for the retrograde transmission In the three cases in which histological findings were reported (Wolferth and McMillan Lequime and Sanabria Winternitz and Langendorf) the degenerative changes were situated in the common bundle near its bifurcation and the upper portions of one or both main branches whereas the A V node and the upper part of the bundle of His were relatively unaffected That this may be more than a coincidence is indicated by the observation that retrograde conduction of automatic ventricular beats has been reported in cases of complete A V block with variable ventricular complexes (Bain) It was pointed out on p 100 that this seems to denote active foci in both main branches The co existence of these two rather rare phenomena would be consistent with and perhaps point to the presence of lesions in the region of and below the bifurcation Further observations are required to establish whether retrograde conduction in complete A V block indicates this particular localization of the lesion

SUMMARY

The retrograde conduction to the auricles of automatic ventricular beats and ventricular extrasystoles in cases of complete A V block must be considered as established This observation implying the presence of retrograde conduction in the absence of conduction in the normal direction was until comparatively recently considered so improbable that various other explanations had been put forward all of which a critical review has shown to be untenable On the other hand this seemingly unlikely occurrence becomes under standable if it is related to the relevant physiological observations on unidirectional block and on facilitation of conduction by impulses passing in the opposite direction It is possible that retrograde conduction in complete A V block indicates that the site of the lesion is in the common bundle near its bifurcation and in the upper portions of both bundle branches but further observations are required to substantiate or refute this conclusion

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EXTRASYSTOLES IN GROUPS

Extrasystoles in groups is defined as an arrhythmia in which two or rarely more ectopic beats originating in the same centre follow one another at a shorter interval than that separ ating such groups from each other There is therefore an alternation in cycle length in this arrhythmia while the ectopic rhythm prevails but the ventricular complexes have identical shapes

There are several reasons for the suggestion that this arrhythmia should be considered as a separate entity

Firstly the historical aspect As two beats succeed one another at a comparatively short interval this group being separated from the following one by a longer interval this arrhyth mia forms one variety of bigeminal or coupled rhythm In the chapter on coupling it is pointed out that for a considerable time great confusion prevailed about the kind of arrhythmia to which the term bigeminy should be applied While the reader is referred to that chapter it should here be recalled that originally Wenckebach wished to restrict the use of this term to that variety of bigeminal rhythm in which the two ectopic beats originated in the same ectopic focus a contention which was abandoned when it became established that in the great majority of instances such rhythm is due to a sinus beat followed by an extrasystole The arrhythmia discussed in the present section therefore constitutes what Wenckebach called true bigeminy In view of the former confusion about the connotation of this term however it was considered inadvisable to revive this name and extrasystoles in groups was suggested instead (Scherf and Romano)

Secondly this arrhythmia is one instance of repetitive impulse formation in one centre Repetitive response to various kinds of stimuli in particular to continuous ones has become realized as an important phenomenon particularly in neurophysiology and also in cardiac physiology Its importance regarding the mode of origin of ectopic beats is fully dealt with in the chapter on Mechanism to which the reader is referred

Thirdly while this arrhythmia is rather uncommon in clinical experience it is by no means rare in experimental investigations We believe that clinically it will be encountered more frequently if records are examined more consistently for this disturbance

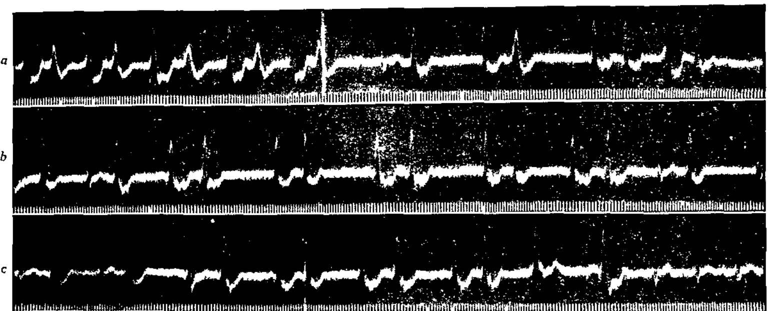


FIG 94.—All tracings lead 3. The record was obtained immediately after the intravenous injection of 0.4 gramme of quinine bihydrochloride. Between the strips *a* and *b* as well as between *b* and *c* about twenty contractions are omitted. *a* the beginning shows ventricular tachycardia with alternating shape of the QRS complexes. The middle shows the abrupt ending of this tachycardia about thirty seconds after the injection; after one bigeminal group consisting of a ventricular extrasystole coupled to a normal sinus beat, extrasystoles in groups occurred. *b* and *c*. Extrasystoles in groups followed by restoration of sinus rhythm (end of *c*). Time base 0.04 second. From SCHERF and ROMANO (*Am. r. Heart J.*)

Experimentally extrasystoles in groups were seen in instances of digitalis intoxication (Kobacker and Scherf Scherf 1927) during the topical application of barium chloride or strophanthin (Scherf and Romano) or after the intravenous injection of acetylcholine followed by atropine (Scherf Chick *et al*) In man this type of irregularity was found in respect of auricular as well as of ventricular ectopic beats (MacKinnon Rachmilewitz and Scherf Scherf and Romano)

Fig 94 provides an example It was recorded in a patient suffering from Extrasystolie a paroxysmes tachycardiques (*see* p 237) During the tachycardia alternation of the QRS complexes was observed After the intravenous injection of 0 4 gramme of quinine bihydrochloride typical extrasystoles in groups occurred until finally sinus rhythm was restored (end of Fig 94c) A few minutes later the tachycardia reappeared Fig 95 was obtained from a dog after the sub epicardial application of strophosid to the conus of the right ventricle For a considerable time each normal beat was followed by four right ventricular extrasystoles Warming of the area to which strophosid had been applied resulted in an increase in the number of ectopic beats which occurred as extrasystoles in groups with alternation in the cycle lengths between successive beats The lengths of successive cycles measured 0 32 0 34 0 37 0 31 0 39 0 31 0 38 0 32 0 39 second etc *In our opinion the last mentioned observation strongly supports the view that these extra* systoles are due to repetitive impulse formation in a centre (see Chapter on Mechanism p 503)

Alternation of cycle length also occurs often during auricular flutter elicited by faradiza tion or by the topical application of aconitine We do not see any difference in principle between this type of grouping of impulses during auricular disorders of rhythm and the extrasystoles in groups described earlier in this section

Grouped discharges are also a well known phenomenon in neurophysiology For example chemical stimulation of nerves of frogs (Brink Bronk and Larrabee) and injury of mammalian nerves (Adrian) are known to produce this type of response This is more fully discussed in the chapter on Mechanism (p 503)

SUMMARY

Extrasystoles in groups is defined as an arrhythmia in which two ectopic beats origin ating in the same centre follow one another at a shorter interval than that separating such groups from each other The three reasons for the suggestion that this arrhythmia should be considered as a separate entity are discussed Reported instances of this disturbance of rhythm experimental as well as clinical are reviewed and illustrated by personal obser vations

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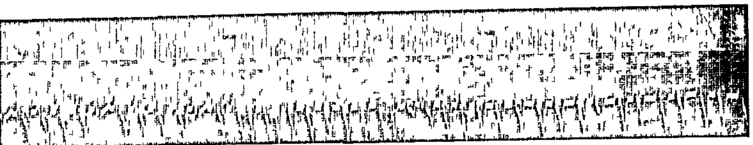
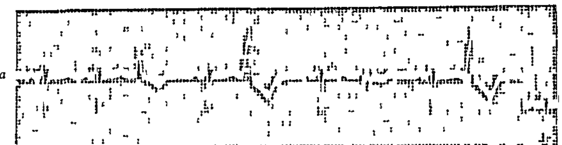


FIG 95.—From an experiment on a dog. After the sub-epicardial application of strophosid to the conus of the right ventricle an arrhythmia was recorded whereby one sinus beat was followed by four right ventricular extrasystoles (beginning of the record). Warming of the area of application of strophosid resulted in extrasystoles in groups. Beginning and end of warming indicated by black lines. For further explanation see text.



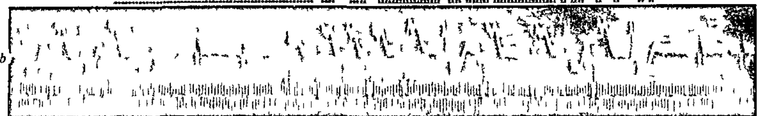


FIG 96.—*a* Lead 3. Four ventricular extrasystoles each of a different shape. *b* Lead 3. Extrasystoles originating in two ventricular foci and occurring in series. At times the ectopic rhythm shows alternation.

MULTIFORM EXTRASYSTOLES

A large proportion of extrasystoles auricular as well as ventricular show a remarkable constancy of form over long periods sometimes amounting to many years As already referred to they are found in otherwise healthy subjects and their presence certainly does not signify myocardial disease though it does not exclude it The inference is that they originate in the same focus which is likely to be small and which at an early stage of electrocardiography was thought to be situated in the specific tissue (Lewis and Silberberg) It is easily understood that such a small focus of presumably only one or a few abnormally irritable cells is well compatible with an otherwise healthy myocardium (*see also* chapter on Mechanism)

If on the other hand extrasystoles of varying shapes are encountered the presence of several abnormal foci or of associated intra ventricular disturbances of conduction or both has to be postulated From this it may be inferred that such multiform extrasystoles are more likely to occur in patients with more extensive myocardial changes Clinical experience in fact shows that they indicate myocardial disease Thus this variety of extrasystoles is frequently found in coronary sclerosis diphtheria with myocardial necrosis or myocarditis—to quote a few instances

Digitalis may lead to the occurrence of multiform extrasystoles but only in patients with myocardial disease (*see* section on Digitalis)

As such extrasystoles of varying shape have to be assumed to arise in several foci they are also called multifocal by some authors We prefer the term multiform (or varyform or polymorphous) since the presence or degree of associated disturbances of intra ventricular conduction cannot be separated from the varying site of origin as far as the electrocardiographic appearances are concerned Mahaim (1931 p 425) pointed out that this term polymorphe (multiform) should refer only to ventricular extrasystoles of varying form and should not be employed for instances in which a combination of extrasystoles originating in different portions of the heart are found in the same patient (for instance auricles and A V node) for the latter variety he suggested the term polytopic While we concur with this view of Mahaim we will also use multiform for auricular extrasystoles with varying shapes of the P waves Clinically multiform (or varyform) extrasystoles of ventricular origin are much the more important

The diagnostic importance of multiform *ventricular* extrasystoles has been stressed by various authors D Irsay in a series of a hundred patients with ventricular extrasystoles (66 uniform 34 multiform) found that the percentage of pathological changes in the myocardium was considerably greater in patients with multiform than in those with uniform premature beats Whereas diseases not involving the myocardium were not accompanied by varyform though sometimes by uniform extrasystoles multiform ones were always associated with myocardial disease Similar views regarding the diagnostic and prognostic significance of multiform extrasystoles were held by others (Peel Avezzu and Chini) Such extrasystoles of various shapes sometimes occur in series and were thus called anarchie ventriculaire (Clerc and Levy Mahaim 1928 1931) Their unfavourable prognostic significance is exemplified by the epithet terminal (Gallavardin Dieuaide and Davidson)

Figs 96 and 97 provide examples Fig 96a obtained from a patient of sixty four with coronary sclerosis and angina pectoris who had not received digitalis shows four ventricular extrasystoles each of a different shape Fig 96b recorded from a patient with coronary sclerosis sixteen days before death (no digitalis treatment) shows ventricular extrasystoles occurring in series and originating in two foci at times there was alternation in the shape of such ectopic beats There was marked arrhythmia of the ectopic rhythm even if successive beats arose from the same site

Fig 97 obtained from a man of sixty seven with congestive heart failure due to cor onary sclerosis a few days before death shows multiform ventricular and also auricular extrasystoles There was no digitalis treatment

Sudden death is not uncommon in patients with multiform ventricular extrasystoles due presumably to ventricular fibrillation

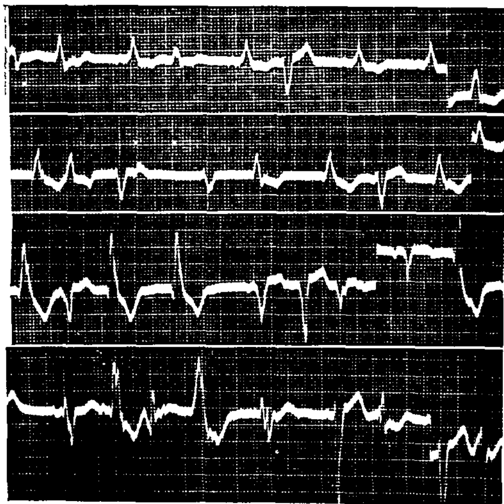


FIG 97 —The three standard leads and lead CR-4 Auricular and multiform ventricular extra ystoles

Varyform ventricular extrasystoles are particularly common in association with pro nounced disturbances of intra ventricular conduction that is in complete A V and in bundle branch block Experimentally they were recorded in experiments in which both bundle branches were severed or damaged (Wilson and Herrmann 1921) Clinically lesions of bundle branches were found histologically in cases in which multiform ventricular



Fig 98 —Multiform ventricular extrasystoles in series in a patient with complete A V block

Fig 99 —Top tracing lead I bottom tracing lead CR-4 Multiform ventricular extrasystoles in series in a patient with complete A V block

extrasystoles had been associated with bundle branch block records (Mahaim 1931) They were also observed in patients with complete A V block as illustrated by Figs 98 and 99 (*see also* Scherf)

Fig 98 was obtained from a patient with complete A V block due to coronary sclerosis Every automatic beat was followed by a series of two to ten ventricular extrasystoles show ing continually changing forms

Fig 99 was recorded in a woman of sixty two with complete A V block Adams Stokes attacks and pronounced albuminuria In the top tracing the first automatic beat is followed by five ventricular extrasystoles with continually changing shapes in the bottom tracing the pronounced differences in the bizarre shape of the several ectopic beats are illustrated Digitalis had not been given The patient died two days after the record was taken

The prognosis in patients with complete A V block and multiform extrasystoles is grave death due to ventricular fibrillation may supervene at any moment It seems reasonable to assume that the same lesion which produced the A V block is also the cause of the multiform ectopic beats The giving of quinidine is dangerous in patients with com plete A V block since it may precipitate extrasystoles and ventricular fibrillation (*see* section on Quinine p 290)

Every transitional stage between multiform extrasystoles multiform ventricular tachy cardia and ventricular fibrillation can be observed so that Gallavardin s term prefibri latoire for such ectopic ventricular arrhythmias seems most apt (*see* Mahaim 1931 p 424)

Denolin reported an interesting observation made in a man of sixty with complete A V block in whom attacks of paroxysmal ventricular tachycardia with varying shape of the ectopic ventricular beats could be precipitated by exercise His paper to which the reader is referred contains references to several further published instances of paroxysmal ven tricular tachycardia in patients with complete A V block

Ventricular tachycardia is one mechanism which may produce Stokes Adams attacks in patients with complete A V block this occurrence is commoner than formerly assumed The same pathological lesion may thus produce A V block ventricular tachycardia and Stokes Adams attacks

Multiform *auricular* extrasystoles are illustrated in Fig 100 which shows four records obtained from three different patients They reproduce auricular extrasystoles and shifting pacemaker with continual change in the shape of the P waves This type of auricular extrasystolic arrhythmia is often the precursor of auricular fibrillation (Langeron) an experi ence which we could often confirm

SUMMARY

Whereas the common variety of auricular and ventricular extrasystoles with constant shape of the ectopic beats does not denote myocardial disease extrasystoles with varying shape in the electrocardiogram are practically always associated with myocardial disease Their occurrence is favoured by concomitant digitalis treatment This variety of extra systoles is termed multiform or varyform or polymorphous extrasystoles The ventri cular variety carries a serious prognosis which is even more grave if this arrhythmia is associated with more pronounced disturbances of intra ventricular conduction (bundle branch block complete A V block) The auricular variety is often the precursor of auricular fibrillation

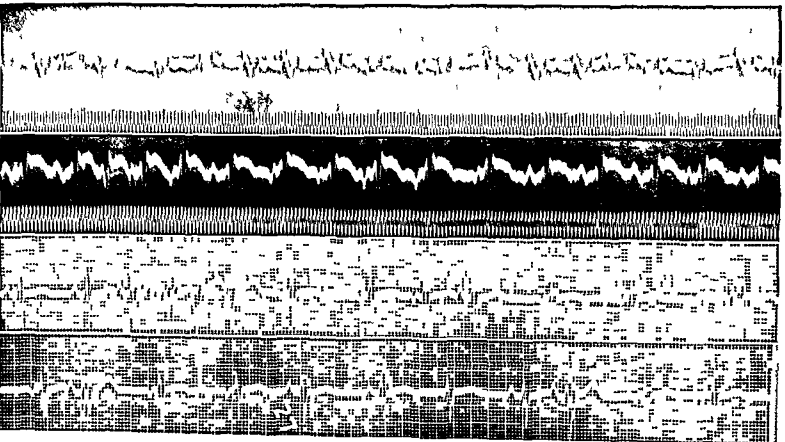


Fig 100 —All records lead 3 obtained from three different patients Auricular extrasystoles with shifting pacemaker and continual change in the shape of the P waves multiform auricular extrasystoles

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Fig 105 top tracing shows an instance of parasystole with simple interference in which two successive ectopic beats occur at two places the ectopic cycle length thus directly measurable was 1 12 and 1 09 seconds (rate 53 and 55 per minute) that of the sinus beats 0 84–0 86 second (rate 70–71 per minute)

Parasystole with simple interference while uncommon is perhaps not quite as rare as the small number of published cases would indicate and might be found more often if longer records were taken and analysed from this point of view It has been estimated that its incidence is about 1 in 1 200 electrocardiograms in a general hospital In 1932 only eleven cases could be collected by Faltitschek and Scherf including five of their own In the attached table particulars are given of the forty nine cases of which we are aware including eighteen hitherto unpublished instances in which we believe the diagnosis to have been established Only those cases were included in which the diagnosis of parasystole could be made with certainty It will be seen that this arrhythmia was somewhat more frequent in men than in women amongst the forty seven cases in which the sex incidence is reported were thirty one men

TABLE 2 VENTRICULAR PARASYSTOLE WITH SIMPLE INTERFERENCE

No	Author	Age	Sex	Cardiac Condition	Rate S A	Rate Ectop
1	SINGER AND WINTERBERG (1920)	20	m	Enlargement left ventricle	71	60
2	WINTERBERG (1923)	52	m	Aortitis	92–120	47–46
3	WINTERBERG (1923)	56	f	Arteriosclerosis and Hypertension	92–95	55
4	SCHELLONG (1924)	37	m	Nephritis one year previously circulatory system normal	53–64	34–35
5	ZANDER (1927a)	40	f	Mitral incompetence	92	41–42
6	SCHERF AND SCHOTT (1930)	63	m	Coronary sclerosis	63–96	53–55
7	FALTITSCHEK AND SCHERF (1932)	30	f	Mitral and aortic valv dis	109–117	89
8		56	m	Coronary sclerosis	130	83
9		63	m		81–92	61 53
10		47	m		88	60
11		33	f	Mitral valvular disease	92	48–49
12	HOLZMANN (1934)	61	m	Advanced congestive heart failure	64–67	60
13		61	f	Hypertension bigeminy	90	46
14		76	f	Advanced congestive heart failure aur fibrillation	—	58 60
15	ECKEY (1936)	70	m	Advanced congestive heart failure	66	70
16	HILL AND CAMERON (1936)	59	m	One month after coronary thrombosis	56–60	4 –46
17	ECKEY (1937)	38	f	Normal	55–69	40–45
18		25	m	(? familial)	83	35
19		54	m	After influenza mild diabetes	67–68	51–57
20	VEDOYA AND BATTINI (1939)	12	f	Normal	109–133	133–139
21	ECKEY (1939)	24	m	After septicaemia Otherwise heart normal	68–80	34–35
22		18	m	Not stated	67–78	46
23	VEDOYA (1944)	50	m	Arteriosclerosis	69–87	54–55
24		48	m	Normal	74–87	38–40
25		51	m	Hypertension	73–100	33–39
26	HOLZMANN (1945)	72	f	Coronary sclerosis cong heart failure	71–76	42–46
27	VEDOYA (1946)	45	m	Right bundle branch block Syphilis	91–109	37–34
28	VEDOYA DUMAS AND URDAPILLETA (1948)	23	f	After acute gastro-enteritis	51–57	38 39

VENTRICULAR PARASYSTOLE WITH SIMPLE INTERFERENCE—*Cont*

No	Author	Age	Sex	Cardiac Condition	Rate S A	Rate Ectop
29	VEDOYA DUMAS AND URDAPILLETA (1948)	37	f	Normal but seven months after confinement toxaemia of pregnancy	*ca*85	50
30	GENTILE (1950)	43	m	Normal but one month after pneumonia	*ca*60	35–38
31	GALLAVARDIN AND FROMENT (1950)	45	f	Rheumatic mitral valvular disease	60–80	61–63
32	SCHERF AND SCHOTT	68	f	Carc recti	71	50
33		56	m	Coronary sclerosis	78	45
34		53	m	Hypertension	82	50
35		34	f	Mitral stenosis auric fibrillation	65*	50
36		?	?	Coronary sclerosis auric fibrillation	82	41
37		52	m	Hypertension	98	61
38		71	m	Coronary sclerosis	70	44
39		48	m	Hypertension	74	32
40		?	?	Hypertension	84	41
41		69	m	Coronary sclerosis	6?	32
42		68	m		71	36
43		70	m	Atheromatosis	75	28
44		74	f	Myocardial infarction	84	31
45		69	m	Hypertension	66	28
46		53	m	Coronary thrombosis	85	34
47		66	m	Coronary sclerosis	68	31
48		66	m	Alcoholic cirrhosis coronary sclerosis	70	21
49		56	m	Coronary sclerosis	96	50

* Average ventricular rate

The ectopic rate tends to be slow but may vary between twenty one and eighty nine (disregarding Vedoya and Battini s case which shows exceptionally high S A and ectopic rates) Some relationship seems to exist between the rates of the two centres the slow ectopic rhythm of 34 was found in a patient with a sinus rate of 53–64 whereas the fast ectopic rhythm with a rate of 89 occurred in a case in which the sinus rate was 109–117 A similar relationship between the rates of the underlying A V rhythm and that of an artificially produced ectopic rhythm was also seen experimentally (Scherf 1926 Scherf and Chick) but clinically as the table shows does not hold good for all cases

Changes in rate of the sinus rhythm may be associated with changes in the same direction of the ectopic rate (Scherf and Boyd 1950)

Diagnosis

The main diagnostic criteria have already been outlined above in this section (p 153) and the varying coupling of the ectopic beats and the simple mathematical relations between the inter ectopic intervals were stressed as the most important features of this arrhythmia If the ectopic cycle length is directly measurable and a parasystolic mechanism is to be diagnosed the inter-ectopic intervals must be multiples of the ectopic cycle length It was also emphasized that only those cases can be considered to be parasystole with simple interference in which—in addition to the above criteria—it can be shown that all impulses of both the sinus and the ectopic centre which fall outside the refractory period of the preceding beat yield responses All these points require some qualifications and amplifications which are also of physiological interest

Coupling If the ectopic rate is slower than the sinus rate—and this is a prerequisite for

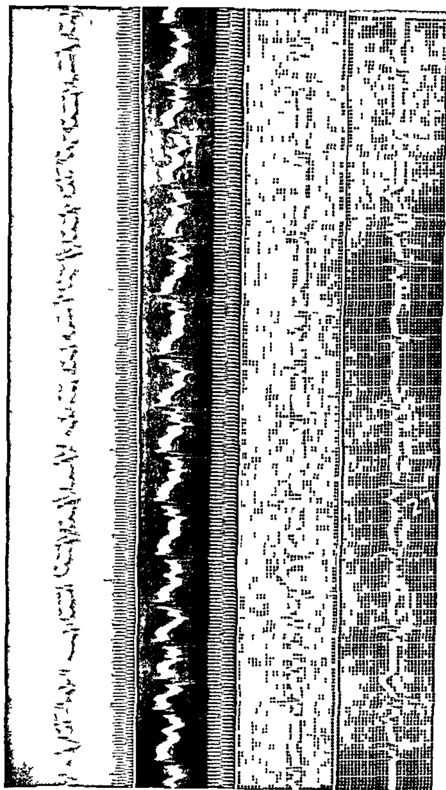


Fig 100—All records lead 3 obtained from three different patients Auricular extrasystoles with shifting pacemaker and continual change in the shape of the P waves *multiform auricular extrasystoles*

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CHAPTER III

PARARRHYTHMIAS

INTRODUCTORY REMARKS

Pararrhythmias represent a group of arrhythmias in which two (or rarely more) centres concurrently and independently produce impulses which yield contractions of the whole heart or parts of the heart without disturbances of conduction of the normal impulse being responsible for the arrhythmia It follows from this definition that the best known instance of the presence of two independent rhythms namely complete A V block does not fall within the category of pararrhythmias

At first sight it would seem surprising if not impossible that a condition of pararrhythmia as defined should exist for it is one of the fundamental laws of cardiac physiology that the centre of impulse formation with the highest rate dominates the rhythm of the whole heart In the normal heart this is the sino auricular node and although all parts of the specialized conducting system have the capacity of impulse formation though at lower rates the sino auricular stimuli destroy all immature impulses in the other parts of the conducting system In certain circumstances however these normal relations may be altered in such a way that two or more centres independently produce effective stimuli

Two main groups of pararrhythmias may be distinguished An automatic centre situ ated with rare exceptions in a ventricle may produce impulses interfering with those of the normal pacemaker producing an arrhythmia termed parasystole or a faster atrio ventri cular rhythm may co exist with a slower sino auricular rhythm the resulting arrhythmia being termed *dissociation with interference*

PARASYSTOLE

The idea that certain arrhythmias may be due to the rhythmic activity of two indepen dent centres of impulse formation was put forward at an early stage of research on disturbances of cardiac rhythm Thus Wenckebach (1903) used the term pararrhythmia for certain extrasystolic arrhythmias with persistence of the basic cardiac rhythm and ascribed certain dissociations and interferences of rhythm to the activity of two independent auricular centres (Wenckebach 1906 Case V same case 1914 IV 3 p 100) or postu lated two functionally dissociated parts of the venous musculature (1907 Case VIII p 6) *These conceptions are no longer tenable The first case could be shown to be an* instance of dissociation with interference (*see* below) the second was found by Wenckebach himself not to be amenable to a satisfactory analysis by the methods then available He con sidered however the possibility that extrasystoles are caused by interference of two auto chthonous rhythms (Wenckebach 1907)

That the common bigeminal pulse may be due to the interference of two rhythms was mentioned by several writers (for example Lauder Brunton Siciliano) but without any proof for this conception Cushny as a result of experimental observations wrote that it was tempting to assume such a mechanism in the common clinical variety of bigeminal action but declared it was surrounded with difficulties and adhered to the view that the extrasystole in the bigeminal heart action is in some way the result of the previous contrac tion

Fleming (1912) seems to have been the first to explain in more detail extrasystoles with accurate coupling as resulting from the activity of an independent ventricular centre of impulse formation By measuring venous and radial tracings he found that the extrasystoles occurred in one record every 1 8 second and in another every 1 6 second the ventricular rate of the independently beating ventricles being 30–40 and concluded This at once suggests that the ventricles are following a rhythm set by two pacemakers one at the sino auricular node producing physiological beats and another at an irritable focus in the ventricle which is rhythmically discharging stimuli at the customary rate of ventricular stimulus production thus giving rise to extrasystoles Fleming already recognized that such a conception would make it difficult to explain the presence of a compensatory post extrasystolic interval since the faster sino auricular impulses would be expected to destroy the immature impulse in the automatic ventricular centre This apparent difficulty might be explained by supposing that the irritable focus in the ventricle which gives rise to rhythmical extrasystoles lies in what may be called a backwater of the primitive cardiac tissue and while stimuli can stream down this backwater physiological stimuli passing down the main channel are unable to disturb the point where ventricular stimuli arise Fleming s paper does not seem to have attracted much attention at the time and his remarks are quoted not only because they are of a certain historical interest but also because they foreshadow one of the main problems which later gave rise to a good deal of controversy namely the application of this theory to the explanation of extrasystoles with accurate coupling

The development of this conception that extrasystoles are due to the rhythmic activity of an ectopic centre is due to Kaufmann and Rothberger s series of important papers published between 1917 and 1923 The starting point was an accidental observation (1917) In experiments on dogs and cats which had been undertaken in order to study auricular extrasystoles artificially produced in different phases of diastole rhythmical stimulation of the *auricles* with a rate different from the spontaneous heart rate produced extrasystoles *which contrary to expectation were accurately coupled to the preceding physiological* beat This was due to the fact that the extrasystoles were conducted to the sino auricular node thereby producing a shift of the S A rhythm The two rhythms are therefore linked by this shift of the S A rhythm The number of extrasystoles depended on the relation between the rate of the S A rhythm and that of artificial stimulation

Rhythmical stimulation of the *ventricles* on the other hand produced a different kind of arrhythmia Since ventricular ectopic impulses are not usually conducted backwards to the S A node the S A rhythm proceeds undisturbed by the extrasystoles which therefore occurred at different phases of diastole in other words with varying coupling With ventricular extrasystoles too an allorhythmia occurred that is an arrhythmia consisting of recurring identical groups of normal and ectopic beats The number of sino auricular and that of ectopic beats in each group depended on the relation between the rates of the sino auricular and that of the ectopic rhythm such groups were far more complicated than in the case of auricular extrasystoles and often two or more ectopic beats followed in succession When the lowest common multiple of the interval between two successive S A beats and that between two successive ectopic beats was reached the same grouping started afresh The same considerations hold good for those auricular extrasystoles which are not conducted backward to the S A node but are followed by a compensatory post-extrasystolic interval

The further development of this conception and its application to clinical cases (Kaufmann and Rothberger 1919a 1920a) led these authors to postulate the following conditions by way of underlying mechanism

1 If an ectopic centre produces rhythmic impulses with a rate lower than that of the S A node it has to be postulated that the ectopic centre is guarded against the destruction by the faster S A stimuli of its impulses Kaufmann and Rothberger termed this mechanism protective block or entrance block

2 If an ectopic centre produces impulses with a rate higher than the S A rate an ectopic rhythm or ectopic tachycardia would result unless some of the ectopic impulses were prevented from becoming effective A blocking of such impulses between the centre of their formation and the myocardium termed exit block was therefore postulated Such exit block would be additional to the protective block the presence of which has to be postulated also in this variety of parasystole since the normal rhythm does not influence that of the ectopic centre

While it will be shown below that this conception of a rhythmic activity of an ectopic centre proved most fruitful for the analysis of certain rare cases of ectopic arrhythmias it must be emphasized that Kaufmann and Rothberger s attempt to explain by this hypothesis the clinically common form of extrasystolic arrhythmias with accurate coupling of the extrasystoles soon met with severe criticism and has now universally been discarded To postulate as an auxiliary hypothesis as did Kaufmann and Rothberger (1922) in order to explain the constancy of the coupling of the extrasystoles a tendency of the rates of the normal and the ectopic rhythm to occur in simple mathematical relations to one another obviously is a *petitio principii* and remains unacceptable even if in some proved instances of parasystole a certain parallelism between these two rhythms was observed both clinically and experimentally The current explanation of extrasystoles with accurate coupling was at the time and still is that they are in some way precipitated by the preceding beat and the objection was raised almost immediately against Kaufmann and Rothberger s auxiliary hypothesis that the simple mathematical relationship between the rates of S A and ectopic rhythm is the *result* and not the *cause* of the accurate coupling (Mobitz Scherf 1924)

We propose to make a fundamental distinction between ectopic beats with accurate coupling and those not standing in a fixed time relation to the preceding beat Only the former group of ectopic beats assumed to be in some way precipitated by the preceding beat should in our opinion be considered extrasystoles in the strict sense of the term The differentiation between extrasystolic and automatic beats is discussed in more detail in the chapter on the mechanism underlying extrasystolic beats

It was also emphasized that only longer records can be used for analysing the mechanism of ectopic arrhythmias since interpretations based on short tracings are open to serious fallacies (Iliescu and Sebastiani Schott 1927) The criticism of Iliescu and Sebastiani however went too far in certain respects as stated later by Lewis in whose laboratory they worked

Kaufmann and Rothberger s great merit is that by their painstaking analysis of numerous experimental and clinical records they established that certain cases of ectopic arrhythmias are due to the co existence of two independent centres rhythmically discharging effective impulses This results in an interference of two independent rhythms the S A rhythm and the ectopic rhythm jointly producing an ectopic arrhythmia Such centres are active side by side —hence the prefix para in parasystole and pararrhythmia

A parasystolic mechanism should be suspected in those cases of ectopic ventricular arrhythmias in which

1 the coupling of the ectopic beats varies

2 the length of the intervals between two consecutive ectopic beats stand in simple mathematical relations to one another

3 The presence of combination (summation fusion) beats showing in the electro cardiogram forms intermediate between those of beats produced by either centre alone tends to support the diagnosis Such beats are due to the simultaneous or nearly simultaneous activation of the heart by the two centres and therefore are expected to occur at such moments at which an impulse is due from each of the two centres

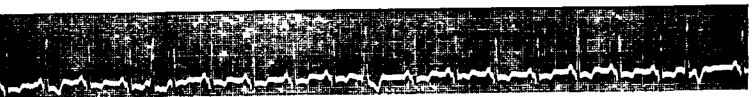
Two main forms of parasystole are recognized In the first variety every impulse of either centre becomes effective if it falls outside the refractory period of the preceding contraction The resulting arrhythmia is termed parasystole with simple interference The second variety differs from the previous one in that some of the ectopic impulses which fall outside the refractory period of the preceding beat fail to yield a response such impulses are believed to be blocked in some way between the ectopic centre and the myocardium (or fail to be initiated), and the resulting arrhythmia is therefore termed parasystole with exit block In both varieties a protective entrance mechanism guarding the ectopic centre from the impulses of the other centre has to be postulated

Parasystole with Simple Interference of Two Rhythms without Exit Block

This arrhythmia which was first described by Singer and Winterberg in 1920 may be illustrated by Fig 101 The record shows sinus rhythm with ectopic beats of ventricular origin The sinus beats are characterized by well developed P waves preceding at a normal interval the QRS complexes These consist of distinct Q waves and slightly slurred R waves which are followed by distorted S T segments with inverted T waves Beats No 2 5 11 and 19 are ventricular ectopic beats occurring in different phases of diastole their Q waves are smaller their R waves higher wider and more slurred and their final deflections more deeply inverted The first ectopic beat (the second beat of the record) occurs so late in diastole that nearly the whole of the P wave of the sinus beat due at the time had already been inscribed The second ectopic beat (Beat No 5) is interpolated Beat No 16 is intermediate in shape between the sinus and ectopic beats that is a combination beat it resembles the sinus beats more than the ectopic ones and it has to be assumed that the ventricles were activated mostly by the sinus impulse [With combination beats the exact time of the occurrence of the ectopic beat cannot be determined If as in the case of beat No 16 the combination beat resembles the sinus beats more than the ectopic ones it has to be assumed that the ectopic impulse activated the ventricles a few hundredths of a second later than the sino auricular one the reverse holds good for combination beats approximating in the electrocardiogram the appearance of the ectopic ones in which case the ectopic impulse must have become effective in the ventricle slightly in advance of the sino auricular one A more accurate determination of the time relations in combination beats between the conducted and the ectopic impulses was possible in a case with right bundle branch block in which the ectopic centre was situated in the right ventricle (Vedoya 1946)]

The occurrence of the ectopic beats in various phases of diastole that is the varying coupling and the presence of combination beats suggest the possibility of a parasystolic origin of the ectopic beats and measurement confirms it since it proves the rhythmic activity of the ectopic centre The sinus rhythm has a cycle length of 0 74–0 78 second (rate 77–81 per minute) The interval between the first and second ectopic beats (Beats No 2 and 5) which are separated by two sinus beats measures 1 97 seconds the longer intervals between the second and third (Beats No 5 and 11) and that between the third and fourth (Beats No 11 and 16) ectopic beats are 3 94 and 3 92 seconds that is double the interval between the first and second one The interval between the last two ectopic beats (Beats No 16 and 19) equals that between the first two (1 98) It follows that the inter ectopic intervals* measured 1 97–1 98 seconds or a multiple of that length (double) measurement also shows that all ectopic beats which fall outside the refractory phase of sinus beats yield a response just as all sinus impulses occurring outside the refractory phase of the ectopic beats become manifest In long records of this patient these conditions were found to be invariably

* Inter-ectopic intervals are the intervals between two consecutive ectopic beats separated by one or more intervening sino-auricular beats Ectopic cycle length as used below in this chapter is defined as the interval between two ectopic beats following in succession



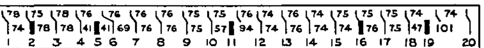


FIG 101 —Lead 2 Parasystole with simple interference The diagram below the tracing illustrates the mechanism of the arrhythmia The figures indicate intervals in hundredths of a second (except the bottom row which indicates consecutive numbers of ventricular beats)



FIG 102 —Lead 2 Parasystole with simple interference



FIG 103 —Lead 2 Parasystole with retrograde conduction of some automatic beats

present and the assumption is thus justified that the arrhythmia is due to the interference between the sino auricular and a slower independent ectopic ventricular rhythm (shortest inter ectopic interval 1 96 seconds corresponding to a rate of about 30 per minute)

Fig 102 obtained in a case of hypertension illustrates a similar condition At first sight the record might give the impression of the common variety of extrasystoles but closer inspection reveals that the coupling of the extrasystoles varies Disregarding the middle portion of the reproduced record its measurement as well as that of other tracings of the same patient shows that the inter ectopic intervals varied between 1 68 and 1 74 seconds the cycle length of the sinus rhythm between 0 80 and 0 84 second The long interval be tween the third and the fourth ectopic beats in Fig 102 measures 6 98 seconds that is four times 1 74 Three intervening ectopic impulses failed to yield a contraction because as measurement shows they occurred during periods in which the ventricles were in the refrac tory phase of the preceding sinus beat

Fig 103 obtained from a sixty six year old man with coronary sclerosis illustrates another instance of parasystole The diagnosis is suggested by the varying coupling of the ectopic beats which is immediately apparent and is confirmed by measurement The cycle length of the sinus beats is 0 88 second (rate 68) the inter ectopic interval 1 98 seconds (rate 31) During the long inter ectopic interval recorded in the centre of the tracing one ectopic impulse failed to yield a response as it occurred during the refractory period of a sinus beat This long inter ectopic interval measures 4 10 seconds and thus is considerably longer than twice the—otherwise constant—inter ectopic interval of 1 98 seconds This lengthening of the longer inter ectopic intervals was invariably encountered in this parti cular case A similar observation was reported by Vedoya (1944 Case 3) His tentative explanation of these time relations is mentioned below in this chapter

Another feature of this case is that some of the ectopic beats were conducted in a retro grade direction to the auricles This is evident because of the occurrence of sharply inverted P waves *in the ascending limb of the first second and fourth ectopic beat* The observation that such retrograde conduction was confined to those ectopic beats which occurred com paratively early in the diastole of the preceding sinus beat suggests that it is due to the pres ence of a supernormal phase of conductivity

This possibility has also to be considered in another observation illustrated in Fig 104 The record was obtained in a sixty six year old man with alcoholic cirrhosis and advanced coronary sclerosis Parasystole is present sinus rhythm (cycle length 0 82–0 88 second rate 68–73) co existing with an automatic ectopic ventricular rhythm The inter ectopic intervals measure 2 84 seconds on an average (2 80–2 87 seconds average ectopic rate 21) While generally the post ectopic intervals are compensatory on several occasions they are lengthened with a consequent shift of the sinus rhythm In Fig 104 three automatic beats are shown The first of these has a coupling of 0 72 second the post ectopic interval is compensatory The post ectopic intervals after the second and third automatic beats are lengthened by 0 06 and 0 08 second respectively and the sinus rhythm is shifted accordingly after these beats The T waves of these two automatic beats contain a P wave which falls outside the expected sequence of the sinus P waves The most likely explanation seems to be that on such occasions the automatic beat was conducted in a retrograde direction to the auricles and probably as far as the S A node Such retrograde conduction was observed only with automatic beats having a coupling of between 0 44 and 0 64 second which suggests that in this case too the phenomenon was due to a supernormal phase of conductivity

Since in the three foregoing examples no two ectopic beats occurred in succession at least one sinus beat being interspersed between them the rate of ectopic impulse formation could not be directly determined It is possible though unlikely in the instances described that the observed shortest inter ectopic intervals might be multiples of the ectopic cycle length

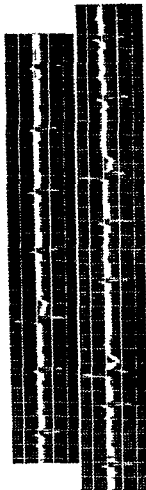


FIG 104 —Lead 3 Parasystole with retrograde conduction of some automatic beats and consequent shift of the sinus rhythm The two records are continuous



FIG 105 —Lead 2 Top record Parasystole with simple interference and two automatic beats in succession Bottom record Continuous bigeminy with accurately coupled extrasystoles observed in the same case From SCHERF and SCHOTT 1930 *Klin Wschr*

Fig 105 top tracing shows an instance of parasystole with simple interference in which two successive ectopic beats occur at two places the ectopic cycle length thus directly measurable was 1 12 and 1 09 seconds (rate 53 and 55 per minute) that of the sinus beats 0 84–0 86 second (rate 70–71 per minute)

Parasystole with simple interference while uncommon is perhaps not quite as rare as the small number of published cases would indicate and might be found more often if longer records were taken and analysed from this point of view It has been estimated that its incidence is about 1 in 1 200 electrocardiograms in a general hospital In 1932 only eleven cases could be collected by Faltitschek and Scherf including five of their own In the attached table particulars are given of the forty nine cases of which we are aware including eighteen hitherto unpublished instances in which we believe the diagnosis to have been established Only those cases were included in which the diagnosis of parasystole could be made with certainty It will be seen that this arrhythmia was somewhat more frequent in men than in women amongst the forty seven cases in which the sex incidence is reported were thirty one men

TABLE 2 Ventricular Parasystole with Simple Interference

No	Author	Age	Sex	Cardiac Condition	Rate S A	Rate Ectop
1	Singer and Winterberg (1920)	20	m	Enlargement left ventricle	71	60
2	Winterberg (1923)	52	m	Aortitis	92–120	42–46
3	Winterberg (1923)	56	f	Arteriosclerosis and Hypertension	92–95	55
4	Schellong (1924)	37	m	Nephritis one year previously circulatory system normal	53–64	34–35
5	Zander (1927a)	40	f	Mitral incompetence	92	41–42
6	Scherf and Schott (1930)	63	m	Coronary sclerosis	63–96	53–55
7	Faltitschek and Scherf (1932)	30	f	Mitral and aortic valv dis	109–117	89
8		56	m	Coronary sclerosis	130	83
9		63	m		81–92	61 53
10		47	m		88	60
11		33	f	Mitral valvular disease	92	48–49
12	Holzmann (1934)	61	m	Advanced congestive heart failure	64 67	60
13		61	f	Hypertension bigeminy	90	46
14		76	f	Advanced congestive heart failure aur fibrillation	—	58 60
15	Eckey (1936)	70	m	Advanced congestive heart failure	66	70
16	Hill and Cameron (1936)	59	m	One month after coronary thrombosis	56–60	4_ 46
17	Eckey (1937)	38	f	Normal	55–69	40–45
18		25	m	(? familial)	83	35
19		54	m	After influenza mild diabetes	62–68	51–52
20	Vedoya and Battini (1939)	12	f	Normal	109–133	133–139
21	Eckey (1939)	24	m	After septicaemia Otherwise heart normal	68–80	34 35
22		18	m	Not stated	67–78	46
23	Vedoya (1944)	50	m	Arteriosclerosis	69–87	54–55
24		48	m	Normal	74–87	38–40
25		51	m	Hypertension	73–100	33–39
26	Holzmann (1945)	72	f	Coronary sclerosis cong heart failure	71–76	42–46
27	Vedoya (1946)	45	m	Right bundle branch block Syphilis	91–109	32–34
28	Vedoya Dumas and Urdapilleta (1943)	23	f	After acute gastro enteritis	51–57	38–39

VENTRICULAR PARASYSTOLE WITH SIMPLE INTERFERENCE—*Cont*

No	Author	Age	Sex	Cardiac Condition	Rate S A	Rate Ectop
29	VEDOYA DUMAS AND URDAPILLETA (1948)	37	f	Normal but seven months after confinement toxaemia of pregnancy	*ca*85	50
30	GENTILE (1950)	43	m	Normal but one month after pneumonia	*ca*60	35–38
31	GALLAVARDIN AND FROMENT (1950)	45	f	Rheumatic mitral valvular disease	60–80	61–63
32	SCHERF AND SCHOTT	68	f	Carc recti	71	50
33		56	m	Coronary sclerosis	78	45
34		53	m	Hypertension	82	50
35		34	f	Mitral stenosis auric fibrillation	65	50
36		?	?	Coronary sclerosis auric fibrillation	82*	41
37		52	m	Hypertension	98	61
38		71	m	Coronary sclerosis	70	44
39		48	m	Hypertension	74	32
40		?	?	Hypertension	84	41
41		69	m	Coronary sclerosis	62	32
42		68	m		71	36
43		70	m	Atheromatosis	75	28
44		74	f	Myocardial infarction	84	31
45		69	m	Hypertension	66	28
46		53	m	Coronary thrombosis	85	34
47		66	m	Coronary sclerosis	68	31
48		66	m	Alcoholic cirrhosis coronary sclerosis	70	21
49		56	m	Coronary sclerosis	96	50

* Average ventricular rate

The ectopic rate tends to be slow but may vary between twenty one and eighty nine (disregarding Vedoya and Battini s case which shows exceptionally high S A and ectopic rates) Some relationship seems to exist between the rates of the two centres the slow ectopic rhythm of 34 was found in a patient with a sinus rate of 53–64 whereas the fast ectopic rhythm with a rate of 89 occurred in a case in which the sinus rate was 109–117 A similar relationship between the rates of the underlying A V rhythm and that of an artificially produced ectopic rhythm was also seen experimentally (Scherf 1926 Scherf and Chick) but clinically as the table shows does not hold good for all cases

Changes in rate of the sinus rhythm may be associated with changes in the same direction of the ectopic rate (Scherf and Boyd 1950)

Diagnosis

The main diagnostic criteria have already been outlined above in this section (p 153) and the varying coupling of the ectopic beats and the simple mathematical relations between the inter ectopic intervals were stressed as the most important features of this arrhythmia If the ectopic cycle length is directly measurable and a parasystolic mechanism is to be diagnosed *the inter ectopic intervals must be multiples of the ectopic cycle length* It was also emphasized that only those cases can be considered to be parasystole with simple interference in which—in addition to the above criteria—it can be shown that all impulses of both the sinus and the ectopic centre which fall outside the refractory period of the preceding beat yield responses All these points require some qualifications and amplifications which are also of physiological interest

Coupling If the ectopic rate is slower than the sinus rate—and this is a prerequisite for

this form of parasystole without exit block since otherwise the faster ectopic rhythm would dominate the whole heart (regarding two exceptions *see* below)—the longest coupling obviously equals the cycle length of the sinus rhythm The shortest coupling can in sufficiently long records be considered to equal the relative refractory period that is the refractory period of the sinus beats for the ectopic impulses in the individual case (Singer and Winterberg) This provides an additional criterion in the analysis of such cases since the shortest coupling of a manifest ectopic beat equals the relative refractory period in order for a diagnosis of parasystole with simple interference to be made it has to be demonstrated that the latent couplings of all those ectopic impulses which calculation shows to have been produced but which failed to yield a response were shorter than the shortest manifest coupling of an ectopic beat Occasionally an ectopic impulse calculated to occur with a coupling slightly longer than the shortest manifest coupling fails to yield a contraction differences up to 0 03 second can be disregarded in this connexion in view of the variations in the rates of sinus and ectopic rhythms and in the length of the refractory phase also because of the margins of error of measurement an exit block need not be assumed in order to explain the failure of such impulses to produce a contraction (*see* Fig. 102)

A glance at Table 2 will show that the ectopic rhythm usually is considerably slower than the sinus rate in all such cases the arrhythmia manifests itself by occasional ectopic beats occurring singly or in short groups the couplings varying considerably in length If however the rates of the S A and of the ectopic rhythm differ but slightly there is a slow shift between the two rhythms longer periods of one rhythm alternate with longer periods of the other and in such cases the variation in the length of coupling is small Only three instances of this variety are on record In one of Holzmann s cases (Holzmann 1934 Case 1) the rate of the sinus rhythm was 64–67 per minute that of the ectopic ventricular rhythm 60 As a result there was a slow shift of the two rhythms and the couplings of the ectopic beats varied only between the narrow limits of 0 60 and 0 64 second that is within the limits usually accepted for the accurate coupling of the common variety of extrasystoles Holzmann points out that in such a case greater variations in the length of coupling cannot be postulated as a condition for a diagnosis of parasystole but it should be understood that while this is justified for the case in question it is a rare exception This case is remarkable also since in addition to the two centres described a third automatic centre produced effective impulses this was probably situated in the A V node The other two cases showing a small difference in the rates of the two rhythms (Eckey 1936 Vedoya and Battini) present similar features but are as far as we are aware unique in that the rate of the ectopic rhythm was slightly faster than that of the sinus rhythm (*see* table) Parasystole with simple interference—without exit block—with a faster ectopic rhythm is possible only if the difference in rates is very small since otherwise ectopic rhythm or ectopic tachycardia would obviously result

An independent ectopic ventricular rhythm interfering with supraventricular beats in auricular fibrillation has been observed in three cases (*see* table)

Ectopic cycle length and inter-ectopic intervals (For the definition of these terms *see* above p 154) The rate of impulse formation in the ectopic centre can be ascertained with the greatest degree of certainty in those cases in which two ectopic beats follow one another in succession without a sinus beat intervening as in Fig 105 In such cases the ectopic rate is directly measurable and a diagnosis of parasystole is greatly facilitated and can be considered established if the longer intervals between consecutive ectopic beats which are separated by one or more sinus beats are multiples of the ectopic cycle length For a variety of reasons however the inter ectopic intervals are not always *exact* multiples of the ectopic cycle length The first reason is that the rate of the ectopic rhythm is not absolutely constant though usually its variations are smaller than those of the S A rhythm Moreover it was found already by Kaufmann and Rothberger and subsequently by others (Singer

and Winterberg Schott 1927 Holzmann) that the longer inter ectopic intervals are a little shorter than a multiple of the ectopic cycle length This is due to the fact that with two ectopic beats following in succession there is slight delay in the conduction of the second impulse owing to the greater demands made on the conducting path between the ectopic centre and myocardium by the two impulses following in close succession It follows that the manifest ectopic cycle length as it is measured as the interval between two successive beats is lengthened beyond the interval between the formation of the two impulses by the *increase in the conduction time of the second impulse this does not occur if* with several sinus beats interspersed in the longer inter ectopic intervals a longer recovery period is available for the conduction of the second impulse There is some evidence that such disturbances of conduction of the ectopic impulse occur If more than two ectopic beats occur in succession the intervals between successive beats tend to lengthen (*see* this section p 164) Zander (1927a) reported a case of ventricular bigeminy in which at times the coupling gradually increased (from 0 44 to 0 56 or 0 58 second) until one extrasystole failed to occur and the subsequent sinus beat was followed by an extrasystole with short coupling and the same *phenomenon* started anew that is Wenckebach s periods in the conduction of the extrasystoles We have observed a similar case (*see* chapter on Coupling p 199) Schott reported a case of parasystole (1927 Case 2) in which the ectopic cycle length was measurable on five occasions being 0 28-0 29 *the longer interval of* 0 37 second which was found at one place could be shown by calculation to be exactly due to delay in conduction of the second impulse of the ectopic couple

As rare exceptions two observations are on record (Vedoya 1944 Case 3 case illustrated by Fig 103) in which longer inter-ectopic intervals—containing a greater number of sinus beats—were longer than a simple multiple of shorter ones In a way this is the reverse of the time relations just discussed By way of a tentative explanation Vedoya points out that in his case this phenomenon was observed if the ectopic beat terminating *the longer inter ectopic interval had a short coupling to the preceding sinus beat* He believes that in such instances the conduction time of this ectopic beat was lengthened owing to the increased demands upon conduction through partially refractory tissue surrounding the ectopic centre by two impulses (one S A one ectopic) following in quick succession Slight differences in shape of ectopic beats occurring with a short coupling are attributed by him to aberrant conduction of the ectopic impulse through this partially recovered tissue around the centre While Vedoya s view is a plausible explanation for his observation we do not believe that a structurally altered block zone surrounding the ectopic centre should generally be postulated to explain the protective and exit block *In our* opinion these phenomena follow more directly from the mechanism of ectopic automatic impulse formation intensity of S A and ectopic impulses and excitability of the ectopic *centre at different times These aspects are discussed in more detail below* in this chapter and in the chapter on Mechanism (p 518)

With these reservations all inter ectopic intervals must be shown to be multiples of the ectopic cycle length if parasystole is to be diagnosed This is particularly important in regard to shorter inter ectopic intervals in which only one or a few sinus beats are interspersed Strict accuracy cannot be expected owing to some variations in the rate of ectopic impulse formation and conduction which were discussed above and to the margin of error in measurement

It is obvious that if a very long inter ectopic interval is divided *into a multiple of the* ectopic cycle length such calculations become useless with intervals beyond a certain length This limit is reached if the average variations in the length of the ectopic cycle length multi*plied by the number of ectopic cycle lengths supposed to be contained in the long* inter ectopic interval attain the length of the ectopic cycle length because any interval exceeding this limit can be shown as a multiple of a whole number and the average ectopic cycle length ±

its maximum variations Singer and Winterberg who first pointed out these relations gave a simple formula for this $E = x (\pm d)$ if E is the average ectopic cycle length $\pm d$ the maximum variations from this average and x the number of ectopic cycle lengths in the inter ectopic interval This means that the greatest number (x) of the cycle lengths in a long inter ectopic interval which can be used as supporting a parasystolic origin is that which multiplied by the greatest variations (d) from the average of the ectopic cycle length does not exceed the cycle length (E) itself Mobitz postulated for this even stricter criteria (which are admirably presented by Feher) In practice it is often possible to dispense with such calculations if the other criteria for diagnosing parasystole are present and particularly if the ectopic cycle length is directly measurable Greater caution is necessary in cases in which this is not possible and the ectopic cycle length has to be calculated from (shorter and longer) interectopic intervals

In a remarkable case published by Vedoya Dumas and Urdapilleta carotid sinus pressure inhibited the sinus rhythm so that the parasystolic ectopic rhythm alone controlled the heart Experimentally vagal stimulation during parasystole produced by veratrine had the same effect (Scherf and Chick)

Clinical significance

A glance at Table 2 shows that out of forty nine recorded cases of this arrhythmia no fewer than thirty eight had evidence of pronounced structural heart or cardiovascular disease As far as any conclusions can be drawn from a small series the assumption seems justified that this association is not coincidental and constitutes but one sign of such structural alterations of the heart

Auricular parasystole

Parasystole with simple interference between S A and *auricular* ectopic rhythm is very rare and as far as we are aware only four cases are on record in which this diagnosis can be considered established

The most convincing instance is the case published by Jervell (1932) His patient was a man of twenty five without any evidence of heart disease in whom the arrhythmia might have been a congenital anomaly The analysis of long records showed parasystole with simple interference between S A rhythm (cycle length 0 51–0 66 second average rate 90) and an ectopic auricular rhythm originating most probably in a focus in the vicinity of the S A node with an average rate of 50 (cycle length 1 13–1 29 seconds) The couplings of the auricular ectopic beats varied widely (between 0 26 and 0 6 second) All inter ectopic intervals were divisible by the smallest inter ectopic interval which was considered to be the cycle length of ectopic impulse formation only one sinus beat intervening Nowhere did two ectopic beats follow in succession The analysis of such a case is more complicated than if the ectopic rhythm is ventricular in origin since the auricular ectopic beats were usually conducted to the S A node (as is the rule with auricular extrasystoles) thereby causing a shift in the S A rhythm Most of the post ectopic intervals were therefore not compensatory It could be shown that the auricular ectopic centre was protected against the S A impulses and that certain variations in the time relations were due to disturbances of conduction of the ectopic impulse to the S A node and within the auricles

Attinger s case seems to be another instance and although the reproduced records are rather short the diagnosis seems very probable His patient was a woman of eighty four with hypertension and coronary sclerosis There was at first 2 1 block and an ectopic auricular rhythm interfered with the S A rhythm the ectopic rate being a little slower than half the rate of the sinus The ectopic centre was probably situated near the tail of the sinus node Subsequently the 2 1 block disappeared but the ectopic auricular rhythm continued giving rise to what appeared to be auricular extrasystoles they had however the same

shape in the electrocardiogram and occurred at the same (—P)-(—P) intervals as before so that persistence of the parasystolic origin could be assumed The ectopic centre was protectively blocked but as in Jervell s case the ectopic auricular impulses were conducted to the S A node so that the post ectopic intervals were not compensatory

Vedoya (1944 Case 5) published another instance of this rare arrhythmia It was observed in a man of thirty five without any evidence of cardiovascular disease The rate of the sinus rhythm varied between 65 and 81 per minute Frequent auricular ectopic beats were recorded the coupling of which varied between 0 49 and 0 85 second Measurement showed the inter ectopic intervals to be divisible by 1 15–1 24 (average 1 20) and a co existing auricular ectopic rhythm could thus be demonstrated The presence of auricular combination beats supported the diagnosis of auricular parasystole In this case too the ectopic auricular impulses were conducted to the S A node producing a shift of the sinus rhythm

Another possible instance of auricular parasystole is one of Kaufmann and Rothberger s cases (1920a) (Case T M No 881 also same authors 1923)

We have observed only one case of auricular parasystole It concerned a fifty nine year old man with a fresh antero septal infarction due to coronary thrombosis The patient had

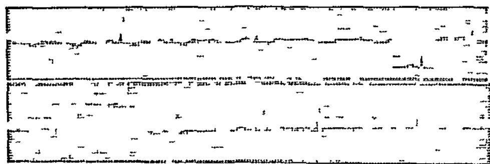


FIG 106 —Leads 1 and 3 Auricular parasystole

received 0 2 gramme of folia digitalis for 8 days Fig 106 shows lead 1 and 3 The second and sixth beats in lead 1 the second sixth and tenth beats in lead 3 represent auricular ectopic beats The coupling varies In the two tracings reproduced in Fig 106 the inter ectopic intervals measure 2 69 2 68 and 2 84 seconds respectively In another record they were 2 68 2 68 and 2 73 seconds

Ventricular parasystole with ectopic centre above the bifurcation of the bundle of His

A unique observation of this form of parasystole has been described by Scherf and Boyd (1950) One of the tracings obtained in that patient a man of seventy with pernicious anaemia is reproduced in Fig 107 It shows sinus rhythm rate about 70 with lengthened P R intervals (about 0 44 second) Premature beats having the same shape as the sinus beats occurred frequently and in Fig 107 the second fifth eighth eleventh and fourteenth beats are easily recognizable as such The interval between two successive premature beats invariably measured 2 58 seconds which would correspond to an ectopic rate of 23 per minute The analysis of other tracings of this patient shows however that this interval of 2 58 seconds actually included two cycle lengths of the ectopic rhythm the rate of which is therefore 46 per minute In the reproduced record only every second ectopic impulse yields a contraction since the remaining ones occurred during the refractory period of the ventricles

A parasystolic arrhythmia has therefore to be assumed in which a sinus rhythm of a rate of about 70 co exists with an ectopic rhythm of a rate of 46 Because of the fact that the ectopic beats have the same shape as the sinus beats the ectopic centre has to be located above the bifurcation of the bundle of His that is in the A V node or the main bundle This also accounts for the absence of combination beats the sinus as well as the ectopic impulses traversed the same paths in the ventricles The ectopic centre was generally protected against the sinus impulses though occasionally sinus impulses occurring at certain intervals after a preceding ectopic beat had to be assumed temporarily to abolish such protective mechanism (*see* original paper)

Parasystole with exit block

This variety differs from the preceding one of parasystole with simple interference in the one respect that some of the ectopic impulses which fall outside the refractory period of the preceding beat fail to yield a response In order to explain this phenomenon it is assumed that such impulses are in some way blocked between the centre of ectopic impulse formation and the myocardium this mechanism was termed exit block (Austrittsblockierung) by Kaufmann and Rothberger (1919a 1920a) Such a mechanism has to be postulated in those cases of parasystole in which the rate of ectopic impulse formation is materially faster than the S A rate since otherwise an ectopic rhythm or ectopic tachycardia would result

The idea that clinically in some cases an ectopic arrhythmia may be due to a parasystolic mechanism with exit block of some of the ectopic impulses tended to be supported by the early observations of Kaufmann and Rothberger (1919a 1920a Case 4) that in patients with attacks of paroxysmal tachycardia the interval between single isolated extrasystoles outside the attacks were multiples of the interval between successive ectopic beats during the attacks It is noteworthy that while for the authors original cases this interpretation has long ceased to be acceptable since they were cases with accurate coupling of the ectopic beats (true extrasystoles) the idea of a parasystolic mechanism with exit block has proved most fruitful in the analysis of other cases and thrown light on certain aspects of impulse conduction

A clear instance of exit block is shown in Fig 108 It shows two sinus beats separated and followed by groups of two ectopic beats following in succession at intervals varying between 0 44 and 0 48 second Two such couples are seen between the two sinus beats and the interval of 0 96 second between the couples is double the interval between the two ectopic beats of the first couple A second longer interval between couples of ectopic beats measuring 0 92 second is seen between the first and second couple following the second sinus beat and here again its length is twice that of the interval between successive ectopic beats These longer intervals are obviously due to the failure of one ectopic impulse to yield a response The case is noteworthy in that the ectopic rate is directly measurable Moreover the last group of three successive ectopic beats reveals evidence of disturbances of conduction of the ectopic impulse the interval between the last two beats of the group having increased to 0 52 second from that between the first two beats which is 0 46 second

An example of parasystole with exit block is given in Fig 109 obtained from a patient with hypertension It shows interference between S A rhythm with a cycle length of 0 67 (rate about 88) and a slower ventricular automatic rhythm (cycle length 1 25–1 28 rate 47–48) The couplings of the ectopic beats vary The ectopic centre is protected against the S A impulses The longer intervals between the second and third and the third and fourth ectopic beats measure 2 5 and 2 62 seconds respectively that is double the shorter interval between consecutive ectopic beats On at least two occasions an ectopic impulse calculated to be due between two S A impulses well outside their refractory period fails to yield a response and the conclusion is warranted that this is due to an exit block operating

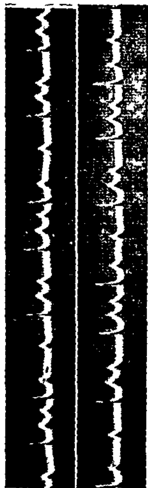


Fig 107—Lead 2 The two strips are continuous Parasystole with ectopic focus above the bifurcation of the bundle of His

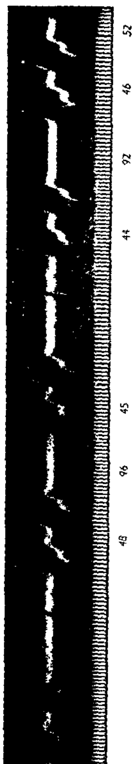


Fig 108—Lead 3 Exit block during ventricular tachycardia Time base 0 04 sec The figures indicate intervals in sec /100

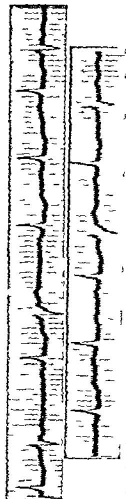


Fig 109—Lead I Parasystole with exit block The two strips are continuous Time base 0 05 sec

on these two occasions The phenomenon of supernormal phase may be responsible for the appearance of ectopic beats only in the early diastole after sinus beats

An exit block has to be assumed in those cases of parasystole in which the ectopic cycle length is shorter than the compensatory pause after an automatic beat since otherwise two ectopic beats would follow in succession An observation shortly reported by Schott (1949) may illustrate this (Fig 110 and Table 3) It was obtained from a seventy six year old

TABLE 3

No	R R	Coupling plus post ectopic Interval	Inter-ectopic Interval	No	R R	Coupling plus post ectopic Interval	Inter ectopic Interval
1	103			24	**65**	205 =	
2	103			25	140	2 × 102 5	
3	**61**	200 =		26	102		301 =
4	139	2 × 100		27	**59**	203 =	5 × 60
5	104			28	144	2 × 101 5	
6	103			29	100		
7	10[illegible]		828 =	30	97		
8	105		14 × 59	31	98		591 =
9	104			32	98		10 × 59
10	104			33	**54**	199 =	
11	**67**	209 -		34	145	2 × 99 5	240 =
12	14[illegible]	2 × 104 5		35	**95**	207 =	4 × 60
13	106			36	112	2 × 103 5	
14	101			37	101		309 =
15	104		843 =	38	**96**	204 =	5 × 62
16	104		14 × 60	39	108	2 × 10[illegible]	
17	103			40	101		497 =
18	103			41	104		8 × 62
19	**80**	208 =		42	104		
20	128	2 × 104		43	**80**	206 =	
21	102			44	126	2 × 103	
22	103			45	106		
23	99		597 =				
24	**65**		10 × 60				

The coupling of the ectopic beats is shown in bold figures
Time relations of a case of parasystole with exit block Lead CR 3 (From SCHOTT 1949)

woman with hypertension a fortnight after a second and five and a half months after the first attack of coronary thrombosis It shows interference between S A rhythm (cycle length 0 97–1 06 rate 56–62) and a ventricular ectopic rhythm All inter ectopic intervals were divisible by 59–62 indicating a rate of ectopic impulse formation of 97–101 per minute An exit block has to be postulated since otherwise an ectopic tachycardia would have resulted It is also seen that the majority of the compensatory post ectopic intervals (measuring 1 08–1 45 second) greatly exceed the ectopic cycle length

Other cases of parasystole with exit block are Case 6 of Faltitschek and Scherf and a case of Feher in which auricular flutter was present

Intermittent parasystole

Intermittent parasystole is defined as a parasystolic arrhythmia in which the ectopic centre produces manifest impulses only intermittently so that the arrhythmia occurs only periodically On the grounds of experimental observations such periodical activity of a parasystolic centre was postulated by Scherf in 1926 (*see* below p 171) and two clinical instances have recently been described by Scherf and Boyd (1950)

Fig 111 obtained from a fifty four year old woman with mild hypertension illustrates this condition The top record shows three ectopic beats followed by two sinus beats

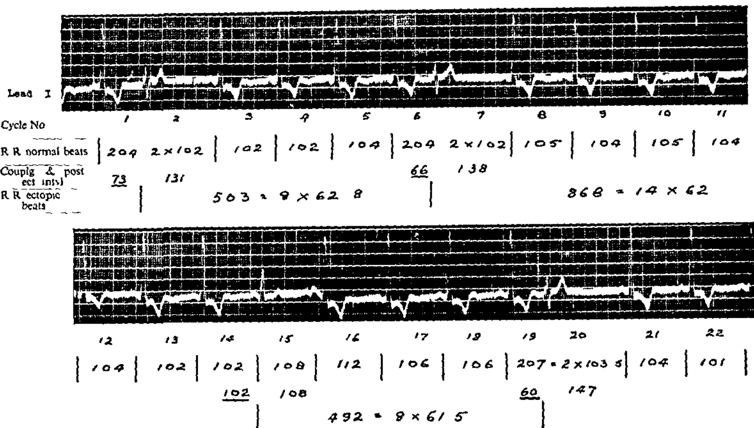


FIG 110—Lead 1 Parasystole with exit block The two records are continuous

which in turn are succeeded by a series of abnormal ventricular complexes The bottom record illustrates essentially the same condition except for the arrhythmia s appearing somewhat more complicated The analysis of this case for the details of which the reader is referred to the original paper showed the arrhythmia to be parasystole between sinus rhythm and an ectopic ventricular rhythm (rates per minute top record sinus 90 ectopic 80 bottom record sinus 80 ectopic 75) Certain beats also of abnormal shape which interfere with the otherwise regular sequence of the ectopic rhythm could be shown to have been sinus beats with aberrant intra ventricular conduction Since the ectopic rhythm proceeds undisturbed by the sinus beats the ectopic centre has to be assumed to have been protectively blocked

The further observation made in both cases that invariably the first ectopic beat of each series was accurately coupled to the preceding sinus beat suggests that the latter initiated

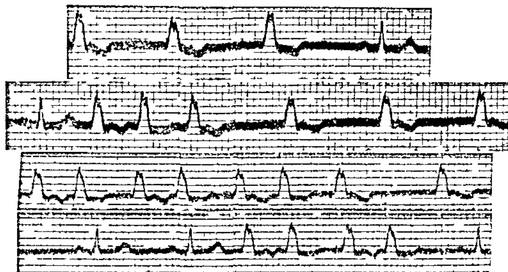


Fig 111 —Intermittent parasystole The two upper and the two lower strips are continuous Time base 0 05 sec

the ectopic arrhythmia in a manner as yet unknown This relationship thus demonstrates another mode of connexion between parasystolic that is automatic and extrasystolic that is dependent impulse formation Further instances of such connexion are discussed below in this chapter and its significance in the chapter on Mechanism (pp 495 519)

The Protective "Block" Exit Block

It was pointed out that a protective block guarding the ectopic centre against interference by the S A pacemaker has to be postulated in *all* cases of parasystole for otherwise an independent ectopic rhythm would not be possible An exit block on the other hand preventing some of the ectopic impulses from becoming effective has to be assumed only in those cases of parasystole in which the rate of ectopic impulse formation is higher than the sinus rate and/or in which not every ectopic impulse calculated to reach the myocardium outside the refractory period of the preceding beat yields a response Both however concern impairment of transmission of impulses in the vicinity of the ectopic centre though in opposite directions and certain features which these two phenomena have in common make their joint discussion desirable

When certain kinds of arrhythmia were first explained as a result of dissociation between auricles or within the S A node (Wenckebach 1906 1907 1914 pp 99 *seq*) no explanation of the underlying mechanism was attempted As early as 1912 Fleming in his paper already quoted foreshadowed later developments by considering the ventricular ectopic focus to be situated in a backwater supposed to be inaccessible to the physiological stimuli passing along the main stream (*see* above in this chapter p 152) Kaufmann and Rothberger introduced the term protective block (Schutzblockierung) placing it somewhere near the ectopic centre (1919a p 233) and considering it to be analogous to the conditions prevailing in cases of complete A V block (1920a p 40) Similar views were held by Winterberg and by Schellong but contested by others (de Boer Griffith) There is however no doubt that a protection of the parasystolic centre exists and it has been conclusively proved experimentally

When Kaufmann and Rothberger first put forward the conception of a protective block (1919a p 233) they based it on the observation of Rothberger and Winterberg made in experiments on dogs that during ectopic ventricular rhythm auricular extrasystoles may be followed by compensatory intervals This is only possible if the ectopic ventricular centre proceeded in its rhythmicity undisturbed by the extrasystole that is was protected against the intrusion of the auricular extrasystole on its way to the ventricles De Boer objected that this observation does not require the assumption of a protective block but could be explained *by the fact that at the time the ectopic ventricular centre was reached by the* extrasystole it was forming the next impulse and thereby refractory to the excitation wave of the extrasystole however this objection though actually admitting some kind of block is certainly not valid for such cases in which a slow independent ventricular pacemaker is active (Wenckebach and Winterberg) Subsequent experimental work demonstrated the presence of a protective mechanism beyond any reasonable doubt

Such investigations became only possible when a method was found experimentally to produce longer chains of ventricular ectopic beats at a comparatively slow rate and originating from one focus This was achieved by electrical or mechanical stimulation of the surface of the exposed heart of dogs in whom the sinus node was clamped and both vagi were cut and who had been given quinine (Scherf 1926) Long chains of ectopic beats were found to persist after such stimulation particularly if the normal pacemaker was inhibited by simultaneous vagal stimulation (Scherf 1927) It could be established that such ectopic beats originated in a circumscribed focus since the shape in the electrocardiogram of such beats depended on the site of stimulation (1926) and their rate increased by warming their site of origin (1927) Proof that such an ectopic centre of impulse formation was protectively blocked against other impulses could be adduced in several ways

Fig 112 illustrates one such experiment 0 4 gramme of quinine had been given intravenously both vagi were cut and a few minutes before the reproduced record was taken the clamps had been removed from the sinus node sinus rhythm returning very shortly afterwards *The right ventricle was stimulated by a series of induction shocks and thirteen* right ventricular ectopic beats resulted the last three of which are reproduced as the first beats in Fig 112 Two spontaneous ectopic beats originating in the same focus followed at intervals of 0 6 and 0 54 second respectively The next three beats are sinus beats the first of which shows a P R interval lengthened to 0 2 from the normal in this experiment of 0 1 second This group is followed by one of six right ventricular beats of the same shape as the previous ones the ectopic rhythm re appearing spontaneously This group is again succeeded by one of three sinus beats followed in its turn by another of five right ventricular ones The ectopic cycle length was on an average 0 5 second and the intervals taken up by the periods of transient sinus rhythm measured 2 05 1 98 and 2 02 seconds that is four times the interval between successive ectopic beats Owing to the occurrence of three sinus beats three ectopic beats failed to yield a response but the rhythmic activity of the

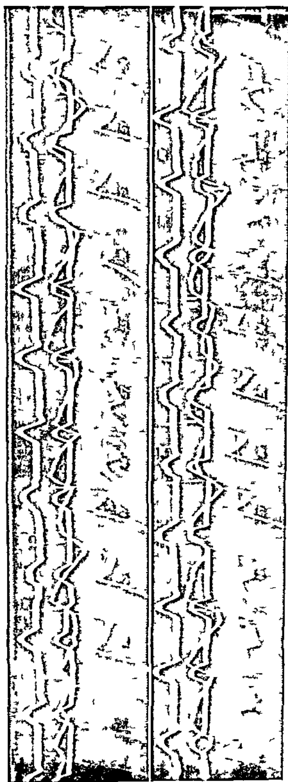


FIG 112.—Parasystole with simple interference experimentally obtained in a dog Tracings from above downward indicate signal (stimulation) suspension records of right auricle left auricle right ventricle electrocardiogram time base 0 02 sec From SCHERF 1926 *Z ges exp Med*

ectopic centre proceeded undisturbed by the sinus beats and the first manifest ectopic beat after the sinus beats occurred at precisely the moment at which it would be expected had no interruption of the chain of ectopic beats taken place This record also illustrates the experimental production of parasystole with simple interference between two rhythms The arrhythmia may periodically be elicited again the rhythm being regular in the interval the term intermittent parasystole was suggested for this condition (Scherf 1926)

In this example the ectopic rhythm came and went spontaneously due to interference by the sinus rhythm In other experiments the ectopic rhythm was artificially interrupted by producing by means of induction shocks a second ectopic rhythm originating in the contra lateral ventricle This resulted in some ectopic beats of the contralateral ventricle during stimulation followed by a certain number of spontaneous ectopic beats originating in the same focus in this same contralateral ventricle the original ectopic rhythm subsequently

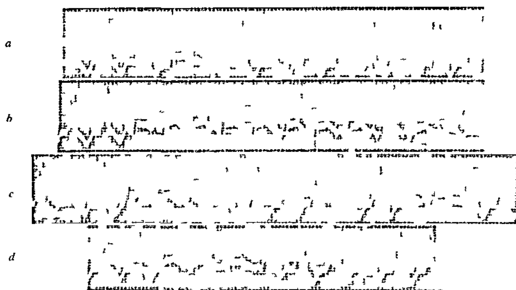


FIG 113 —Parasystole with simple interference produced in a dog by the topical application to the heart of sodium chloride The four strips are continuous

being re established In such experiments it was invariably found that the interval in the original rhythm between the last beat before the interruption and the first beat of the re established rhythm after the interruption equalled exactly a multiple of the cycle length of the original ectopic rhythm or differed from it by half a cycle length but intermediate figures were never found The significance of the difference by half a cycle length will be discussed below in the present context it may be disregarded The conclusion is therefore warranted that during the artificially produced ectopic rhythm of the contralateral ventricle the ectopic focus producing the original rhythm continued undisturbed by the impulses originating in the other ventricle that is was protectively blocked against them (Scherf 1926)

Similar results were obtained if the heart was sensitized with small doses of barium and a ventricle electrically stimulated slowing of the sinus rhythm by vagal stimulation fav oured the occurrence of ectopic rhythms and similar time relations were observed (Scherf 1927)

The same conclusions were arrived at in experiments undertaken with an entirely different method It had been shown by Piccione and Scherf that ectopic beats and ectopic rhythms can be produced by the sub epicardial injection of 0 1 cc of a 10 per cent solution of NaCl Fig 113 is taken from such an experiment and shows an ectopic ventricular tachycardia elicited in this way from the conus of the right ventricle The ectopic rhythm was interrupted at times by a variable number of sinus beats The four reproduced strips marked *a–d* are continuous In the two upper tracings the ectopic cycle length is 0 36 second with remarkable constancy In the top tracing the ectopic rhythm is interrupted by one sinus beat and the interval between the last ectopic beat before and the first ectopic beat after the sinus beat measures 0 72 second that is exactly double the ectopic cycle length The long interval interrupting the ectopic rhythm in strip *b* measures 4 08 seconds (that is 11 times 0 37) In strip *c* the ectopic cycle length had decreased to 0 34 second and the two intervals during which sinus (or combination) beats intervened measure 1 37 seconds (= 4 × 0 342) and 1 00 (= 3 × 0 333) In the bottom strip *d* the ectopic cycle length had increased again to 0 36 second and the interval taken up by the sinus rhythm measures 1 44 seconds (= 4 × 0 36) These measurements show that whenever the ectopic rhythm was interrupted by sinus rhythm the first ectopic beat recurred at a time when it would have been due without interruption of the ectopic rhythm that is throughout the intervening sinus rhythm the ectopic centre retained its rhythmical activity being guarded against extraneous (sinus) impulses by protective block The presence of combination beats is a further proof of the parasystolic character of this arrhythmia

In certain experimental conditions (aconitine intoxication and mechanical stimulation) in which two ectopic ventricular rhythms interfered with one another a double protective block that is a block protecting each of the two centres against the impulses of the other could be demonstrated (Scherf 1930)

While in such experiments parasystole was observed only occasionally in a recent series of experiments Scherf and Chick found that topical application of veratrine to the ventricular surface invariably gave rise to parasystolic arrhythmias in which the ectopic centre was protectively blocked

Fig 114 was obtained from such an experiment Immediately after application of a 0 5 per cent solution of veratrine alkaloid to the conus of the right ventricle an ectopic tachycardia was recorded which interfered with the sinus rhythm The intervals between the last ectopic beat of one and the first of the subsequent group were always multiples of the ectopic cycle length Combination beats occurred frequently

The nature of this protective block has been extensively discussed No single mechanism was found that could be considered responsible for it in all cases

Some kind of a block zone surrounding in some way the centre of ectopic impulse formation was early postulated (*see* above) and is still assumed in more recent work (Doumer Vedoya 1944 Katz) With this conception the same area of block was invoked to account for the exit block a more detailed diagrammatic view of its supposed structure is contained in Doumer s and Vedoya s papers The latter developed an ingenious conception of two zones of refractory tissue surrounding the ectopic centre whereby the degree of refractoriness *of the zone closest to the centre* (Zone B) *is greater than that situated more peripherally* (Zone A) The duration of refractoriness of Zone A is assumed to be less than the cycle length of the sinus rhythm that of Zone B to be longer and only slightly less than the ectopic cycle length Vedoya shows diagrammatically that such conception would explain the mechanism of protective and of exit block also that of the breaking through the protective mechanism of some impulses in certain changes of rhythm such as transition of parasystole into an extrasystolic arrhythmia with extrasystoles of accurate coupling (*see* below p 174) It has to be conceded that a zone of such or a similar kind may exist in some cases not only was the presence of an area of depressed conduction made most probable by

histological findings in some cases of retrograde conduction of automatic ventricular impulses in cases of complete A V block (*see* p 138) and considered likely in cases of return extrasystoles (*see* p 120) but also the location of that area could be shown to be of paramount importance the relation between such arrhythmias and unidirectional block is discussed in the appropriate sections Similar areas may well exist in certain cases of parasystole in the vicinity of the ectopic centre

It is however difficult to imagine a block zone spherically surrounding the ectopic centre and being of a kind that it prevents impulses from reaching the centre from every direction whereas the ectopic impulses could pass this zone in the opposite direction Wachstein s observations of interference of two or more rhythms and of interpolated extrasystoles in isolated Purkinje fibres show that whatever the nature of the block is it is or at least can be situated in a very small area Faltitschek and Schert located it in the cell or group of cells forming the ectopic centre and pointed out that it will depend on the intensity of the S A impulses on the one hand and the irritability of the centre itself whether the S A impulses will break into the centre in a similar way they attributed the presence or otherwise of exit block to the intensity of the automatic ectopic impulse and the irritability of the tissue surrounding the centre Goldenberg Gottdenker and Rothberger found in Purkinje fibres of dogs that condenser discharges stimulating the whole fibre did not disturb the rhythmical spontaneous activity of one of several centres and concluded that the condenser discharges were sub threshold for this centre Again the emphasis is on the relation between strength of stimulus and excitability of the ectopic centre This conception received further support by the more recent observations of Scherf and Boyd (1950) discussed above They indicated that the ectopic centre can be protected either because the stimuli of the other centre are below the threshold necessary to excite the cells of the ectopic centre or because the ectopic centre is less excitable In one particular case (Scherf and Boyd 1950 Case 1) the assumption was justified that only during a temporary increase in excitability of the ectopic centre namely its supernormal phase after emission of an impulse could it be reached by the sinus impulses Because of all these considerations we prefer the term protection to protective block

One difficulty which is encountered if the processes in the centre are visualized more closely in conjunction with the membrane theory of initiation and conduction of impulses and some suggestions about

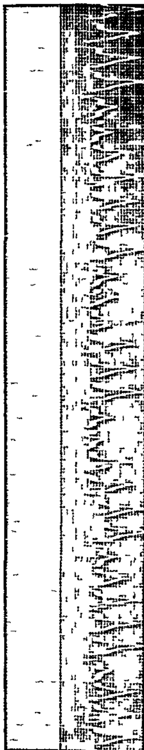


Fig 114 —Parasystole with simple interference produced in a dog by the topical application to the heart of veratrine

a possible solution of this problem are discussed in the chapter on Mechanism (p 518)

While the assumption of some particular kind of blocking mechanism whether structural or functional seems necessary to explain the protection of the ectopic centre in cases in which the automatic rhythm is slow this is not necessary in instances in which the automatic rhythm is fast If the ectopic centre produces impulses at a high rate this itself would account both for the protective and the exit block since the centre would be surrounded by refractory tissue as a result of its fast impulse formation There are good reasons for assuming that in some cases this is the underlying mechanism and that the rate of impulse formation in the ectopic centre is actually higher than the record as such would seem to indicate

Thus it was pointed out above (p 171) that if a chain of ectopic beats was interrupted by an artificially produced number of ectopic beats of the contralateral ventricle the interval between the last beat of the original rhythm before and its first beat after its interruption always equalled a multiple of its cycle length *or differed from it by half a cycle length* From this it can be concluded that the actual rate of ectopic impulse formation was twice that indicated in the record every second impulse being blocked In other experiments irregular ectopic arrhythmias were seen which could best be interpreted by the assumption of a faster underlying ectopic rhythm with 3 2 or 2 1 block between the centre and myocardium or a degree of impairment of conduction analogous to dropped beats (Scherf 1926) Clinical examples indicating disturbances of conduction of the ectopic impulse were mentioned above (pp 161 and 164) but the most convincing instance in this connexion is a case published by Rosenbluth and Winterberg Their patient a thirty nine year old man showed A V extrasystoles and attacks of A V paroxysmal tachycardia In one of such attacks a sudden doubling of the rate was recorded (from 83 to 166 per minute) and the obvious interpretation is that with the slower rate a 2 1 exit block had been present Outside the attack a slower ectopic A V rhythm producing beats with the same shape in the electrocardiogram as those during the attacks interfered with S A rhythm the couplings of the ectopic beats varying between 0 38 and 0 76 second and it could be shown on one occasion that after an attack isolated A V ectopic beats occurred at intervals which were multiples of the ectopic cycle length during the rapid phase of tachycardia

Fig 115 provides another example obtained in an experiment on a dog (Scherf) At the beginning of the record a series of eight ectopic beats is shown elicited in the way described above (p 169) and following one another at intervals of 0 22 second (rate 272 per minute) The rate suddenly dropped to 108 (cycle length 0 55 second) This abrupt change in rate is best explained by a sudden blocking of the ectopic impulses The difference in the height of the three ectopic impulses during slower rhythm as compared with the beginning of the record can be attributed to the pronounced change in rate and does not indicate a change of focus of origin

Failure of impulses to be initiated may also have to be considered as possibly accounting for the change in rate by simple multiples of ectopic rhythms This mechanism has been found in the local oscillatory responses of giant squid nerves in certain experimental conditions (*see* chapter on Mechanism p 510)

Parasystole and Extrasystoles with Fixed Coupling

It was pointed out that if an independent ventricular ectopic centre produces impulses which interfere with the S A rhythm the coupling of such ectopic beats to the preceding beat necessarily varies and that (with very rare exceptions) the varying coupling is one of the cardinal features of this arrhythmia which distinguishes it from the common variety of extrasystoles with fixed (or accurate) coupling In very few cases it could be observed that a



Fig 115 —Exit block recorded in a dog Tracings from above downward indicate signal (stimulation) suspension records of right auricle left auricle right ventricle electrocardiogram time base 0 02 sec

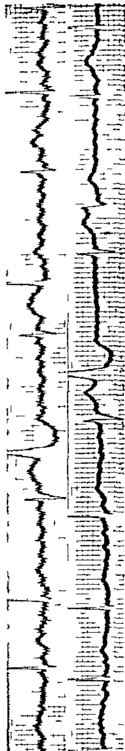


Fig 116 —Parasystole and extrasystoles which occurred only after automatic beats observed during auricular flutter (top record) and auricular fibrillation (bottom record)

parasystole with simple interference changed into an extrasystolic arrhythmia with fixed coupling of the extrasystoles (Scherf and Schott 1930 Rothberger 1931 p 675 Vedoya and Battini) Thus Fig 105 shows in its top tracing parasystole with simple interference the ectopic cycle length being directly measurable (1 09–1 12 seconds) and the couplings of the ectopic beats varying between 0 42 and 0 67 second Other records of the same patient established the parasystolic mechanism of the arrhythmia beyond doubt the ectopic cycle length being measurable in five places at 1 12 seconds the rate of the sinus rhythm varying between 64 and 98 and the couplings between 0 42 and 0 69 second Shortly afterwards continuous bigeminy was recorded the extrasystoles had the same shape in the electrocardiogram and were accurately coupled to the preceding beat the coupling being 0 51 second (*see* Fig 105 bottom strip) and in a longer record comprising 31 beats varying only between 0 50 and 0 52 second This change in the arrhythmia was probably due to the continuing digitalis treatment resulting in disappearance of the protection of the ectopic centre

Vedoya and Battini s case is of special interest since it shows various changes in the kind of arrhythmia the combination of which is extremely rare In their patient a girl of twelve *there was first parasystole with simple interference between an S A rhythm with a cycle* length of 0 45–0 55 second (rate 109–133 per minute) and an idioventricular rhythm which was a little faster (cycle length 0 43–0 45 second rate 133–139 per minute) The small difference in the rate of the two rhythms resulted in their slow shift At several places unusually long intervals were noticed when a ventricular automatic beat failed to occur at a time it was due this was attributed to an exit block * It was then observed that at times a ventricular automatic beat was followed by an extrasystole of the same shape in the electrocardiogram with a coupling of 0 39 second (their Fig 5) or by what appeared to be a combination beat (their Fig 6) Subsequently the ventricular automatic beats disappeared and a bigeminy was recorded with extrasystoles which had identical shape and were accurately coupled to the preceding sinus beat with the same coupling which they previously had in connexion with automatic beats

Such observations show that the same ectopic centre which produces automatic impulses can also produce true extrasystoles with accurate coupling to the preceding beat Similar observations were made by Rachmilewitz and Scherf in cases other than parasystole namely in cases of auricular fibrillation with coupled beats and in a case of sino auricular block and by Scherf and Schott (1932) in a case of complete A V block with ventricular extrasystoles (For the relationship between automatic and extrasystolic impulse formation including the significance of the above observations *see* chapter on Mechanism)

Fig 116 illustrates another combination between a parasystolic arrhythmia and extrasystoles It was obtained in a case of mitral stenosis with auricular flutter and fibrillation *In this case a parasystole was found during five days observation during which the patient* was given large doses of digitalis in order to convert auricular flutter into fibrillation Extrasystoles were recorded having various shapes in the electrocardiogram and following only ventricular automatic beats but never supraventricular ones (Scherf and Schott 1951) The coupling of the extrasystoles was fairly constant and it could therefore be excluded that such beats were supraventricular ones with aberrant ventricular conduction Fig 116 top tracing shows this arrhythmia during auricular flutter the bottom tracing during auricular fibrillation No satisfactory explanation could be found for the observation made in several cases that extrasystoles occurred only after automatic ventricular beats For some

* Closer inspection of their tracings shows that this phenomenon was only observed after ventricular ectopic beats in relation to which an S-A impulse was due either synchronously or very shortly afterwards Vedoya and Battini s observation is better explained by the assumption that the S-A impulse was conducted to the ectopic centre there destroying the stimulus being formed but failed to reach the ventricle owing to being blocked below the ectopic centre This interpretation would be along the same lines as that explaining a similar phenomenon in cases of dissociation with interference (*q v* p 186)

tentative views on the underlying mechanism the reader is referred to the original paper (Scherf and Schott 1951)

In conclusion it can be said that the occurrence of a parasystolic origin in some rather rare cases of ectopic arrhythmia has to be considered as established Not only does this conception offer the best explanation of such cases but it also does not conflict in any way with accepted principles of cardiac physiology On the contrary a more detailed analysis of such cases tends to enlarge and deepen our understanding of the mechanism underlying impulse formation and conduction The main difficulties in connexion with this conception were encountered when the originators of this idea made an attempt to explain by it the common variety of extrasystoles with accurate coupling This having been generally abandoned the distinction between a parasystolic mechanism concerning an ectopic automatic rhythm and extrasystoles in the strict sense of the term being precipitated by the preceding beat has furthered our understanding of the mechanism underlying both these groups of ectopic arrhythmias

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DISSOCIATION WITH INTERFERENCE

Definition and Relation to Parasystole

Dissociation with interference is a condition in which a faster atrio ventricular (or rarely

ventricular) and a slower sino auricular rhythm coexist and in which the slower sino auricular rhythm at times interferes by conducted beats with the faster atrio ventricular one

It follows that this arrhythmia falls within the range of pararrhythmias the heart being stimulated by impulses originating in two independent centres As in parasystole such an arrhythmia is only possible if the centre of the slower rhythm is protected from the faster impulses arising in the other one otherwise the faster atrio ventricular rhythm would dominate the whole heart A V rhythm resulting The essential difference between para systole and dissociation with interference is that in the former a slower ectopic rhythm interferes with a faster sino auricular one whereas in dissociation with interference it is the ectopic—A V—rhythm which is the faster and it is the normal pacemaker which produces the slower rhythm that interferes with the faster ectopic one In these two varieties of par arrhythmia compared with one another the roles of relative rates between sino auricular and ectopic rhythm are reversed and so are for this reason the roles between the centre whose impulses interfere and that whose impulses are interfered with A further funda mental difference between parasystole and dissociation with interference is the periodic linking of both rhythms in the latter

Underlying Mechanism

As already stated a slower sino auricular rhythm can exist side by side with a faster A V rhythm only if the slower centre is protectively blocked against the faster impulses of the other focus If this block is unidirectional and operates only in the retrograde direction from the A V node towards the S A node whereas the spread of the excitation wave in the normal direction remains unimpaired such sino auricular impulses which fall outside the refractory periods of the conducting system and of the ventricles will yield a response from the ventricles How many of the sino auricular impulses will thus become effective in the ventricles depends chiefly on the relation between the rates of the S A and of the A V rhythm the A V conduction time of the S A impulses and the length of the refractory period of the junctional tissues and of the ventricles Those sino auricular impulses which reach the ventricles will temporarily interfere in a twofold manner with the A V rhythm first of all they will cause a premature beat of the ventricles within the otherwise regular se quence of the A V ones and secondly the conducted impulses while travelling through the junctional tissues will interfere with the formation of impulses in the A V node so that the immature impulse there will be destroyed and impulse formation starts anew at the moment when the conducted impulse has left the A V node With these conducted beats and with these only does the slower sino auricular rhythm interfere with the faster A V one and it is with these beats that the two rhythms are linked

Experimental Observations

The occurrence of such an arrhythmia in certain experimental conditions was observed by Cushny as early as 1897 On the grounds of analysis of myocardiographic tracings of auricle and ventricle in dogs recorded during a certain stage of digitalis (strophanthin) intoxication he described it with remarkable clarity as follows

Two independent rhythms may occur in the heart and the contractions of each of the divisions concerned may be perfectly regular in force rate and size This continues how ever only as long as the passage of impulses from the one to the other is blocked As soon as two rhythms occur without any hindrance to their passage from one division to the other the contractions of each become irregular owing to the interference of the transmitted im pulses with the contractions generated spontaneously in each division An impulse may

pass either to the ventricle from the auricle or in the reversed direction (McWilliam Bayliss and Starling)

Returning now to the tracings obtained after digitalis we find that in the first stage we often have the same rhythm in auricle and ventricle throughout In this case the rhythm is auricular the inhibitory action slowing it but not being strong enough to block the impulse passing to the ventricle As the action proceeds the inhibition becomes weaker or more probably the muscular action on the auricle overcomes the inhibitory and the rhythm becomes less slowed than immediately after the injection The auricular rhythm is still however somewhat slower than normal owing to the inhibition The muscular action is more marked on the ventricle and the inhibitory is less powerful Accordingly we find the irritability of the ventricle at last so great that the slow auricular rhythm is no longer sufficient to satisfy it and the ventricle takes up its own rhythm and is therefore now set in motion by two sets of impulses one generated in its own the other derived from the auricular muscle As long as the extraneous impulse reaches the ventricle during its refractory period it will have no effect and if the two rhythms are nearly equal a number of impulses are therefore ineffective In this way the irregularity becomes periodic the periods being longer at first when the rhythms are nearly equal but becoming shorter as they diverge more from each other

In the auricle the condition is similar the same interference of the two rhythms occurring and the same periodic irregularity Occasionally however the auricle is fairly regular while the ventricle is periodic This is because the passage of impulses from the auricle to the ventricle is much easier than in the opposite direction Thus we may have an interference occurring in the ventricle from the clashing of the auricular and ventricular rhythms while the ventricular impulses are unable to pass to the auricle and the latter therefore beats perfectly regularly (P 279)

These relationships were further clarified in the early days of electrocardiography In 1910 Rothberger and Winterberg showed in experiments on dogs that while atrio ventricular rhythm was developing or subsiding a transient stage exists during which the auricles are stimulated by the sinus node and the ventricles respond to A V impulses In a subsequent series of experiments the same authors obtained in 1912 electrocardiographic records demonstrating a dissociated cardiac action with occasional interference of conducted sino auricular beats with an idioventricular rhythm (*see also* the reproduction of such a record in Rothberger 1931 Fig 42)

In 1929 Scherf established that this arrhythmia occurred during a certain stage of aconitine intoxication Fig 117 provides an example It shows A V rhythm periodically interfered with by conducted S A impulses As a result of the injection of aconitine the sino auricular rate was slowed below the A V one the S A rate being 50 and that of the A V rhythm 67 per minute With great constancy one S A impulse is conducted to the ventricles after every two A V beats The R R intervals between a conducted and the subsequent A V beat (0 88) equalled those between two successive A V beats as would be expected (*see* below) (Aconitine also diminished the contractility of the auricles as demonstrated by the absense of excursions of the mechanical record of the auricle Atropine restored immediately both normal rhythm and normal contractility) This arrhythmia was also found experimentally to occur as a result of emetine (Boyd and Scherf unpublished experiments) and quinidine (Korns)

Clinical Observations

The first clinical case of this kind was described in 1906 by Wenckebach who on the grounds of mechanical records alone available at the time gave it a different interpretation but later agreed with the revised diagnosis Wilson described in 1915 an instance of this arrhythmia giving the tracings the interpretation though not the name which is now

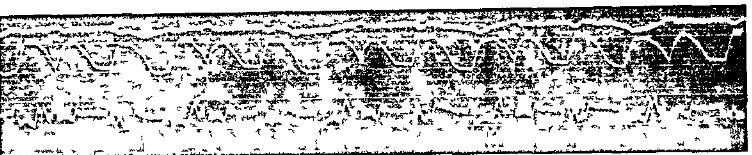


Fig 117.—Dissociation with interference experimentally *produced in a dog by means of* aconitine Tracings from above downward indicate suspension record of right auricle that of right ventricle electrocardiogram (and oesophageal lead) time base 0.02 sec Note the absence of signs of contraction of the auricle being due to high vagal tone The small waves in the auricular suspension record are due to transmitted ventricular contractions

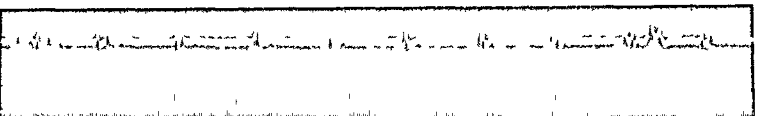


Fig 118.—Lead 2 Dissociation with interference with slow rates of both centres

generally accepted Shortly afterwards cases with the correct interpretation were reported by White and by Heard and Colwell Whether the true mechanism was recognized by Lea in a paper published at that time (1915) seems doubtful

That this condition was recognized as an arrhythmia *sui generis* is largely due to the extensive work of Mobitz (1923a) who called it Interferenzdissoziation and also showed that several other cases described earlier but interpreted in various other ways actually were cases of this kind (cases of Wenckebach Weil Taschenberg Edens) In accordance with Wenckebach Scherf proposed the term Dissoziation mit Interferenz in preference to that of Mobitz (Scherf 1926) best rendered in English as dissociation with inter ference A representative list of published cases of this arrhythmia is contained in the bibliography of this section Of the four cases reported by Stein and Bartlett only Cases 2 and 4 are acceptable without reserve their Case 3 is most probably an instance of this arrhythmia though the reproduced tracing is very indistinct

Three cases of suprarenal tumour are on record in which dissociation with interference was recorded amongst arrhythmias observed during hypertensive crises In this condition the arrhythmias are considered due to the adrenaline circulating in the blood (Burgess *et al* Hegglin and Holzmann Espersen and Jorgensen)

Fig 118 provides an example of this arrhythmia The record was obtained from a patient with hypertension and coronary sclerosis who had been treated with unknown doses of digitalis At the beginning of the tracing an automatic A V beat is seen followed by two conducted sino auricular ones The subsequent seven beats are A V beats the P waves which occur in relation to these beats gradually approach the ventricular complexes then are fused with them and finally emerge after the initial complexes between the R S R and T waves The ninth P wave of the record occurs sufficiently late after the initial ventricular complex of the preceding automatic A V beat (the tenth of the record) to be conducted to the ventricles The tracing shows clearly that the first of the conducted beats gives rise to a premature contraction Subsequently the same cycle of slowly shifting rhythms with occa sional conducted S A beats repeated itself In this instance the auricular rate was about 36 and the A V rate 40 per minute This close proximity of the two rates resulted in a slow shift of the two rhythms whereby most of the S A impulses fell within the refractory period of the automatic A V beats It should be noted that the interval between the last conducted beat and the next automatic A V beat equals that between two successive A V beats This is to be expected in an uncomplicated case of this kind since the conducted impulse destroys on its passage through the A V node the immature impulse being formed there at which moment the impulse formation in the A V node starts afresh with the same rate as during the periods without interference It will be shown below that and why the time relations may be more complicated in some cases

That the A V rhythm should be faster than the S A one may be due to an abnormally slow S A rhythm for instance due to a 2 1 sino auricular block (presumably present in Fig 118) or to an abnormally fast A V rhythm While a sharp distinction between these two varieties as attempted by Dressler (1930) is unacceptable Fig 119 may serve to illus trate this arrhythmia with faster rates It shows dissociation between a faster A V rhythm of 85–88 with a slower S A rhythm of 74–76 per minute The third and seventh S A im pulses are certainly and the second most probably conducted beats Sometimes both the A V and S A rates vary such variations tend to occur in the same direction and are attri buted to variations in vagal tone (Scharf and Weiser Scherf 1926)

Since both the A V and the conducted beats reach the ventricles through the normal paths it is to be expected that their ventricular complexes are the same as is shown in Figs 118 and 119 For two main reasons however the ventricular portions of the conducted beats may differ in shape from those of the automatic A V beats First this may be due to aberrant conduction in the ventricles of the conducted beats owing to inadequate recovery



Fig 119.—Lead 2 Dissociation with interference with faster rates of both centres



Fig 120.—Aberrant intraventricular conduction of a sinus beat in dissociation with interference From Schott 1937b *Guy's Hosp Rep*

of the paths of conduction in the ventricles As in the case of auricular extrasystoles (*see* p 55) this tends to be the more pronounced the sooner after the preceding beat the premature impulse is to be conducted Fig 120 provides an example It shows dissociation with interference between an A V rhythm of 51 per minute (cycle length 1 16 seconds) and a very slightly slower S A rhythm of 50–51 per minute (cycle length 1 17–1 20 seconds) The fifth sino auricular impulse which occurs at the very start of the fifth automatic A V beat is conducted to the ventricles with the lengthened A V conduction time of 0 63 second and gives rise to a ventricular complex the shape of which differs grossly from that of the A V beats The next S A impulse is also conducted but with the shorter P R interval of 0 33 second and its ventricular portion does not materially differ in form from that of the A V beats It is obvious that on superficial inspection the first of these conducted beats may easily be misinterpreted as ventricular extrasystole (*see also* Burchell)

The second reason for a difference in shape in the ventricular portions of conducted and automatic A V beats is dissociation with interference between an idioventricular centre and the normal S A pacemaker Fig 121 shows such a case demonstrating dissociation with interference between an idioventricular centre situated below the bifurcation of the bundle of His and S A rhythm With such a location of the centre of faster impulse formation the ventricular portions of its beats cannot resemble those of conducted beats The rate of the idioventricular rhythm was 94 per minute (cycle length 0 64 second) that of the S A rhythm 85–88 per minute (cycle length 0 68–0 7 second) The long interval in the centre of the tracing between the automatic beats before and after the sinus beats measures 1 76 seconds this is not a multiple of the automatic periods which indicates that there is no protection of the ectopic centre from the sinus beats In addition this figure also shows the first variety of abnormally shaped ventricular complexes namely that of conducted beats due to aberrant conduction the seventh and eighth S A impulses are conducted the seventh with aberrant conduction

Special features regarding time relations

Reasons were given above for the statement that in the uncomplicated case the interval between the ventricular complexes of a conducted and that of the subsequent A V automatic beat equals that between two successive automatic A V ones But this is not invariably the case such intervals sometimes being found shorter sometimes longer than the inter automatic ones The analysis of such differences has thrown some light on the underlying mechanism and is of physiological interest

Shortening of the inter ventricular interval following a conducted beat may be found if more than one conducted beat follow in succession This tends to be particularly pronounced if the A V conduction time of the first conducted beat is considerably longer than that of the second Such an instance is contained in Fig 120 in which the interval following the conducted beat P_5–R_6 is shortened to 0 88 from the usual 1 12–1 16 seconds inter automatic interval of this case During that time the rate of the S A rhythm remained unchanged and the shortening of the interval R_6–R_7 can be shown to be due to the difference in A V conduction time between 0 63 second of the first and 0 33 of the second beat But shortening of this interval is also observed if no second conducted impulse follows the first and this is of considerable physiological interest Fig 122 gives an example It shows dissociation with interference between a faster A V rhythm (R R cycle length 0 86–1 00 second rate 60–70 per minute) (disregarding the abnormally long cycle 17 for reasons given below) and a slower S A rhythm (P P cycle length 0 94–1 16 second rate 52–63 per minute) Some S A impulses are conducted and yield ventricular responses (cycles 1 4 10 13) Cycles 2 11 and 14 all of which follow conducted beats and are themselves certainly not terminated by a second conducted beat are shortened to 0 66 and 0 68 second respectively This phenomenon was first described by Scherf (1926) who established

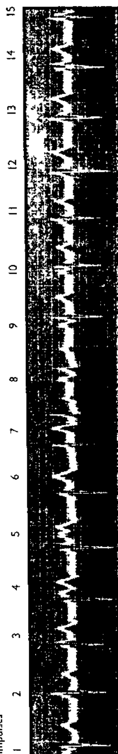


FIG 121 —Disso iation with interference b tween sino auricular and idioventricular rhythms

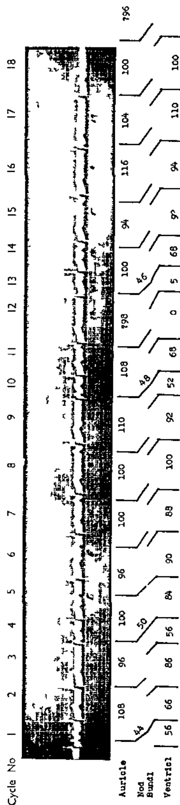


FIG 122 —Dissociation with interference with shortening of the interval following a conducted beat From SCHOTT 1937b *Guy s Hosp Rep*

that it is due to delayed conduction of the conducted S A beat in the bundle of His As the delay takes place below the A V node impulse formation starts in the node as in most cases of this arrhythmia at the moment the conducted impulse has left the node since owing to the infra nodal delay in conduction of the conducted impulse the ventricular excitation of this beat occurs later in relation to the impulse s leaving the node the subse quent interval is bound to be shortened The physiological importance of this observation lies in the fact that it forms one more proof of the occurrence of disturbances of conduction in the bundle of His (cp section on Extrasystoles in A V Rhythm and Return Extra systoles p 102) This interpretation is also supported by the observation that in one case showing this phenomenon other signs of impaired conduction were present namely intra auricular disturbances of conduction lengthening of the A V conduction time and aberrant conduction in the ventricles (Schott 1937a) Similar observations are contained in a paper by Luten and Jensen though differently interpreted by the authors

Contrariwise the interval following a conducted beat may be *lengthened* A small degree of such prolongation can be attributed to inhibition of A V impulse formation as a result of the passage through the node of the conducted impulse In some cases however such intervals are far too long for this explanation to be acceptable Fig 123 taken from the same case as Fig 120 demonstrates this phenomenon It shows dissociation with inter ference (rate of A V rhythm 52–55 per minute cycle length R R 1 08–1 16 seconds rate of S A rhythm 46–54 per minute cycle length P P 1 12–1 30 seconds) The first two cycles show the P waves gradually approaching the automatic A V complexes the fourth P wave is fused with the last part of the ventricular complex of A V beat No 4 and this beat is fol lowed by an interval of 1 62 second after which the heart beats in sinus rhythm for the next three beats The question poses itself why did no atrio ventricular beat occur after the usual interval of 1 08–1 16 seconds? The same phenomenon occurred on two other occa sions (cycles 9 and 14) Closer analysis of these and other records revealed that such abnor mally long intervals were observed only if an auricular contraction fell *just* at the *end* or *coincided* with the *beginning* of the automatic ventricular deflections It could be shown that S A impulses falling just in these phases were conducted to the ventricles but failed to yield a response from the ventricles as they were blocked in the lower parts of the conducting system The conducted impulse while passing through the A V node there discharged the immature impulse formation of the next A V impulse starting again when the conducted impulse had left the node However before the next A V impulse could become effective the next S A impulse stimulated the ventricles as well as the auricles It will be observed that all three abnormally long intervals are in fact terminated by conducted beats Thus in these instances in which the impulse formation in the A V node apparently suddenly fails to occur the condition actually reveals itself as a further degree of impairment of conduction in the bundle of His a sino auricular impulse though passing through the node being blocked in the bundle These relationships could be proved by calculation and were found to be accurate within 0 01–0 02 second (Schott 1937b) The same mechanism is responsible for the abnormal length of cycle 17 in Fig 122 and for a similar phenomenon in Vedoya and Battini s case though interpreted by these authors as due to a sudden exit block (*see* preceding section on Parasystole p 176) A similar explanation was put forward by Winternitz who observed only one instance of this phenomenon which he attributed to a certain critical length of the R P interval intermediate between shorter ones not resulting in a conduction of the S A impulse and longer ones with the customary inverse relationship between R P and the subsequent P R intervals A similar view was expressed by Korth and Schrumpf (1936) but no time relations were given A further instance of this arrhythmia has recently been reported by Gentile (Case I)

While in such instances the site of block has to be located in the main bundle a case of

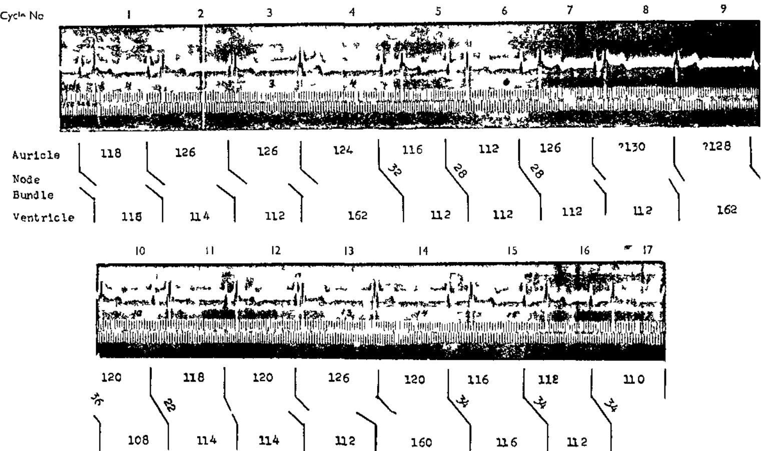


FIG. 123.—Dissociation with interference with lengthening of the interval following a conducted beat owing to disturbances of conduction in the bundle of His. The two strips are continuous. From SCHOTT 1937 b. *Guy's Hosp. Rep.*

dissociation with interference has been reported by Burchell in which disturbances of conduction of S A impulses occurred in the right or the left bundle branch Which of the two bundle branches failed to conduct depended on the interval between the P wave of the con ducted beat and the R wave of the preceding A V beat with R P intervals of 0 18–0 28 second left with those of 0 30–0 39 second right bundle branch block configuration of the conducted beat was recorded The atrio ventricular conduction time of beats with left bundle branch block was considerably longer than of those with right bundle branch block Different recovery rates of the two bundle branches was assumed by way of a hypothetical explanation of this observation and the possibility of a supernormal phase of recovery in conductivity of the left bundle branch block was considered

Whatever the reason in an individual case of dissociation with interference may be that causes the A V rate to exceed that of the S A pacemaker the prerequisite for this kind of arrhythmia is that the rate of effective impulses produced by the A V node exceeds that of the rate of S A impulses being capable of being conducted at least as far as the A V node Thus halving of the effective S A rate by 2 1 sino auricular block is one of the various conditions that may give rise to this arrhythmia (*see* above Fig 118) The same holds good in cases of 2 1 A V block in which the rate of the automatic rhythm is faster than half the S A rate (Dressler 1929) In this connexion the observation is of interest that dissociation with interference occurred in a case of paroxysmal tachycardia with 2 1 A V block At one stage probably as a result of digitalis dissociation with interference ensued when the A V rate became a little faster than *half* the auricular rate (P P intervals 0 28–0 3 second auricular rate 200–214 per minute R R intervals 0 52–0 57 second A V rate 105–115 per minute) Owing to increasing disturbances of conduction below the A V node of the conducted impulses some of them failed to yield a ventricular contraction and abnormally long intervals in the ventricular rhythm resulted (Schott 1946)

Dissociation with interference between a faster ectopic auricular rhythm and S A rhythm *cannot be considered as established Mobitz s attempt (1923b) to explain in this way a case* reported and differently interpreted by Kaufmann and Rothberger (Case 1) is unconvincing and was rightly criticized by Schellong (1924)

Diagnosis

The recognition of this arrhythmia is only possible by graphic methods On routine clinical examination it is bound to be mistaken for sinus rhythm with extrasystoles a regular underlying rhythm is found which is occasionally disturbed by premature beats and the conclusion would seem obvious that the regular rhythm is sinus rhythm and the prema ture beats are extrasystoles Graphic records particularly an electrocardiogram reveal that the regular dominant rhythm actually is an ectopic (in most cases A V) rhythm and what had given the impression of being extrasystoles actually are conducted S A beats If an electrocardiogram is available the main difficulty is to distinguish it from return extrasystoles (for a short summary of the main points *see* Herrmann and Ashman) this can only be achieved with certainty if longer records are taken An independent auricular rhythm is one of the essential features of dissociation with interference and the diagnosis of this arrhythmia is supported if the P waves are upright in leads 1 and 2 or leads 1 2 and 3 The shape of the P waves in the presence of an independent auricular rhythm also serves to distinguish dissociation with interference from auricular parasystole Other points regard ing the differential diagnosis are contained in the section on Return Extrasystoles (*q v* pp 111 119) The correct diagnosis may be missed even electrocardiographically particu larly if only shorter records are used and a typical record was misinterpreted as showing ventricular escape as recently as 1948 (Kirby)

Clinical Aspects

Conditions which are known to give rise to this arrhythmia are large doses of digitalis infectious diseases (endocarditis pneumonia) and impairment of the normal impulse formation in the sino auricular node presumably due to impairment of its blood supply in other cases no aetiological factor can be traced The chief and often sole complaint of the patient is palpitation which may be very troublesome it is caused by the conducted beats Fainting and giddiness may occur in cases with marked sinus bradycardia The condition is often transient One unusual instance in which this arrhythmia was recorded in a young child after scarlet fever and observed over several years was reported by Schott (1951)

In many cases this arrhythmia does not require treatment If it can be assumed to result from digitalis treatment the drug should of course be temporarily discontinued In one case in which no digitalis had been given it was found that *small* doses of this drug (0 125 mg Digoxin twice daily) abolished the arrhythmia and restored sinus bradycardia (Schott 1937a)

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SUMMARY

Pararrhythmias are defined as a group of arrhythmias in which two (or rarely more) centres independently produce impulses which yield contractions of the whole heart or parts of the heart without disturbances of conduction of the normal impulse being respon sible for the arrhythmia

The prerequisite which makes it possible for two independent rhythms to co exist is the protection of the centre with the lower rate of effective impulse formation against the intrusion of the stimuli produced by the faster centre Failing such a mechanism which was termed protective (or entrance) block the faster centre would dominate the rhythm of the whole heart

Two main groups of pararrhythmias are distinguished (1) An automatic centre situ ated with rare exceptions in a ventricle may produce impulses interfering with those of the normal pacemaker this variety is called **parasystole** (2) a faster atrio ventricular rhythm

may co exist with a slower sino auricular one the resulting arrhythmia being termed **dissociation with interference**

Parasystole

Two varieties of this arrhythmia may be distinguished (a) parasystole with simple interference and (b) parasystole with exit block

In parasystole with simple interference the impulses of a slower ectopic centre interfere with those of the faster sino auricular node in such a way that the stimuli of either yield *ventricular contractions if they fall outside the refractory period of the preceding beat* The main criteria of this arrhythmia are the varying in length of the coupling of the ectopic beats to the preceding S A beat the simple mathematical relationship between the inter ectopic intervals (which are defined as the intervals between consecutive ectopic beats separated by one or more S A beats) the divisibility of the inter ectopic intervals by the ectopic cycle length where the latter is directly measurable as the interval between two ectopic beats occurring in succession the occurrence in the electrocardiogram of combination (fusion summation) beats intermediate in shape between those of beats produced by either centre alone and being indicative of the simultaneous or nearly simultaneous activation of the heart by impulses originating from both centres Some qualifications and amplifications of these diagnostic criteria are discussed

A list of forty nine cases is given in which this diagnosis can be considered to have been established including eighteen personal hitherto unpublished instances It is pointed out that as far as this small number makes it possible to draw any conclusions this arrhythmia tends to occur in patients with structural heart disease

Four reported cases of parasystole with simple interference in which the ectopic centre was situated *in an auricle* are discussed and one personal observation is added

One instance of ventricular parasystole with the ectopic centre located above the bifurcation of the bundle of His is discussed as well as the experimental production of parasystole by means of veratrine

Parasystole with exit blocrk differs from the foregoing variety in that the rate of impulse formation in the ectopic centre is faster than that of the S A pacemaker and that some of the ectopic impulses are prevented from becoming effective by a mechanism termed exit block Failing such exit block an ectopic rhythm or ectopic tachycardia would result Several instances of this comparatively rare arrhythmia are given

Observations on *intermittent parasystole* are discussed that is a condition in which parasystole occuurs periodcally

The development of the conception of a parasystolic mechanism of some ectopic arrhythmias is discussed with special reference to the pioneer work of Kaufmann and Rothberger It is pointed out that contrary to the original contention of these authors such a mechanism is unacceptable to explain the clinically common variety of extrasystoles with accurate coupling but that their ideas have stimulated much thought in the analysis of clinical and experimental records of irregular heart action

The nature of the condition underlying protective and exit block is discussed and experiments proving the existence of a protective mechanism are reviewed Regarding the possible mechanism of protective and exit block in clinical cases the various views about its nature are discussed While most authors assume an anatomical substratum located around and in close proximity to the ectopic centre we believe that a diminished excitability of the ectopic parasystolic centre in regard to the conducted impulses is the essential factor underlying such protection We therefore prefer the term protective mechanism or protection to protective block

The rare instances of transition in the same case of a parasystolic ectopic arrhythmia

into an extrasystolic arrhythmia with accurate coupling of the extrasystoles are reviewed The significance of such observations regarding automatic and extrasystolic impulse formation in ectopic centres is emphasized and reference made to the chapter on Mechanism underlying the Origin of Extrasystoles which is devoted to the discussion of this subject

Dissociation with Interference

This is a condition in which a faster atrio ventricular rhythm and a slower sino auricular rhythm co exist and in which the slower sino auricular rhythm at times interferes by conducted beats with the faster atrio ventricular one

As in parasystole protection of the centre of slower impulse formation from the stimuli of the faster centre is a prerequisite but as distinct from parasystole in dissociation with interference the ectopic—A V—centre is the faster and the normal pacemaker the slower centre

If an unidirectional block exists between the A V and S A node operating only in the direction from the A V to the S A node such sino auricular impulses which fall outside the refractory period of the conducting system and of the ventricles will yield ventricular responses and these conducted beats interfere with the otherwise regular A V rhythm With these conducted beats and with these only are the two rhythms linked

The conducted impulses give rise to premature beats and since they destroy the immature impulse in the A V node when passing through the node the interval in the ventricular rhythm following a conducted beat is in the uncomplicated case equal to that between two successive A V beats Since both the conducted and A V beats reach the ventricles through the normal paths the shape in the electrocardiogram of these two kinds of beats is in the uncomplicated case identical

Exceptions to this rule both regarding lengths of intervals and shape of beats are discussed and it is pointed out that the closer analysis of these phenomena is fully in accordance with and has thrown further light on some principles of cardiac physiology Most of these exceptions could be shown to be due to disturbances of conduction of impulses in the bundle of His and/or in the ramifications of the conducting system in the ventricles

The reported clinical instances of this arrhythmia are reviewed and a representative list of published cases is contained in the bibliography of this section

The experimental conditions in which this arrhythmia was observed are reviewed

Clinically the diagnosis can only be made by graphic methods since otherwise it is invariably mistaken for sinus rhythm with extrasystoles Electrocardiographically it has to be distinguished from return extrasystoles and from auricular parasystole

Large doses of digitalis and infectious diseases are the chief known precipitating factors

The condition tends to be transient and in this event no treatment is necessary In other cases temporary discontinuation of digitalis is indicated

CHAPTER IV

THE COUPLING OF EXTRASYSTOLES BIGEMINAL RHYTHMS

Coupling is defined as the time interval between an ectopic beat and the beat preceding it All such ectopic beats are often termed extrasystoles but in our opinion this is undesirable for reasons fully discussed in this book Regarding the definition of coupling of ventricular extrasystoles *see* also p 27 of auricular extrasystoles p 48 for Lewis s terminology (Lewis 1925) p 27

ACCURATE AND VARYING COUPLING

According to their coupling extrasystoles can be divided into two main groups

(1) those with accurate (constant fixed) coupling in which the time interval between the extrasystole and the preceding beat is constant or varies within very narrow or systematic regular limits and

(2) those with varying coupling in which variety extrasystoles occur in all phases of diastole

A sharp distinction between these two groups is justified on historical experimental clinical and theoretical grounds

The varying coupling which characterizes the above group (2) is the hallmark of an automatic ectopic centre of impulse formation co existing with the normal pacemaker the resulting arrhythmias—parasystole—are discussed in the chapter on pararrhythmias (*q v*) The present chapter is confined to the discussion of the above group (1) to which alone in our opinion the term extrasystoles in the strict sense of the word should be applied

BIGEMINAL AND TRIGEMINAL RHYTHMS

Extrasystoles with accurate coupling may occur singly or after a longer or shorter series of beats of the dominant rhythm or after each beat of the dominant rhythm In the last mentioned case the ensuing rhythm often is termed bigeminal rhythm or coupled beats Not infrequently this term is applied rather loosely and gives rise to confusion Used merely *in a descriptive way it denotes a rhythm in which two beats occur within a comparatively* short interval which is preceded and succeeded by a longer pause While in the majority of such cases such rhythm is the result of an extrasystole following each beat of the dominant rhythm this is by no means the only underlying mechanism as will be shown below For the sake of clarity we therefore recommend that if this designation is used at all it be qualified by adding the mechanism responsible for it for example bigeminal rhythm due to ventricular extrasystoles bigeminal rhythm due to every third sinus impulse being blocked on their path to the ventricles etc Some examples of bigeminal rhythm due to mechanisms other than extrasystoles are given later in this chapter

HISTORICAL

Supplementing what has been said in the chapter on Historical Remarks a few words about the development of our conception of bigeminal heart action and pulse may

not be amiss Traube was the first to observe in 1862 what he called zweispitzige Wellen (bifid waves) in blood pressure records obtained after the injection of curare and bilateral vagotomy Subsequently in his paper on the effect of CO poisoning he suggested the term *pulsus bigeminus* as superior to zweispitzige Wellen (Traube 1865–66) In 1872 he encountered in pulse tracings of patients what he called a variation of the *pulsus bigeminus* which he designated *pulsus alternans* namely a succession of high and low pulses in such a manner that a low pulse regularly follows a high pulse and this low pulse is separated from the ensuing high pulse by a shorter pause than that between it and the preceding high pulse (Traube 1872 quoted from *Cardiac Classics* p 591) While Traube succeeded in differentiating the dicrotic pulse from *pulsus bigeminus* and *alternans* a confusion between the two latter had been started which for a considerable time was to obscure the analysis and particularly the prognosis of this group of arrhythmias An added source of confusion about the significance of bigeminal heart action was due to Wenckebach s contention which he maintained for several years (1903 1906) that true bigeminy should only be assumed in cases in which the two beats of the twin contraction were accurately coupled and of an identical nature and that this form of arrhythmia had no connexion with extrasystoles This view was soon contested by Hering (1904 a b) (who attacked Wenckebach in language leaving little doubt about the strength of his convictions and the intensity of his emotions 1904b) and had to be abandoned when it was established by Lewis (1910) that the two beats of the pair originated in different foci

A different kind of terminological confusion has arisen more recently in regard to the word trigeminus Wenckebach (1914) defined tri quadri and polygeminy as arrhythmias in which two three or more extrasystoles respectively follow one another and many authors before and after him have used these terms in this way Of late however the designation trigeminus has been applied to arrhythmias in which one extrasystole followed two normal beats Occasionally the same term has even been applied by the same author to both types of arrhythmias In our opinion the term trigeminus should only be used to denote two extrasystoles following one initiating beat that is as suggested by Wenckebach and others before him Quite apart from the fact that only this way of employing the word is in accordance with the historical development—which originated from Traube s use of the term *pulsus bigeminus* (*see* above and also section on Ventricular Extrasystoles p 33—it is clearly undesirable to use the same word to describe two totally different kinds of arrhythmia Kisch who in 1945 devoted a special study to this question of terminology and to whose paper the reader is referred for particulars about the various ways in which various authors used such terms rightly points out that if the word trigeminus were used to describe two normal beats followed by one extrasystole polygeminy would mean an arrhythmia in which one extrasystole occurs after several normal beats which is clearly nonsensical this justifies our insistence that such terms should only be employed in the sense in which they were originally suggested

EXPERIMENTAL

In contradistinction to the great frequency with which extrasystoles with constant coupling occur in clinical practice in experimental work they are most difficult to elicit Apart from the *topical* application of various compounds the only three methods known to us by which it is possible experimentally to produce this type of arrhythmia with any degree of certainty are in the dog by means of aconitine (Scherf 1929) and by strophanthin combined with the inhalation of a mixture rich in CO_2 (Goldenberg and Rothberger 1931) and in the rabbit by clamping of the carotids after sensitization of the animal with barium (Schott 1934) (*See also* chapter on Nervous System p 225) Of these the first is the one that has been most extensively studied Fig 124 provides an illustration Fig 124a was recorded from a dog after the injection of such small doses of aconitine that no effects

could be traced either in the mechanical (suspension) records of the right auricle and ventricle or in the electrocardiogram which shows sinus rhythm Stimulation of the right vagus in the neck immediately produced ventricular bigeminy with extrasystoles of constant shape and constant coupling following each sinus beat (Fig 124b)

It will be shown elsewhere in this book (chapter on Mechanism) that extrasystoles in the strict sense of this term originate in a circumscribed focus where they are precipitated by the preceding beat The behaviour of the coupling proved to depend on the path which the impulse of the initiating beat had to traverse in order to reach the centre of extrasystolic impulse formation Fig 125 is taken from one of these experiments (Scherf 1930) Fig 125a shows a continuous bigeminal rhythm in a dog following injection of aconitine Each sinus beat was followed by an extrasystole which originated in the left ventricle the extrasystoles had the same shape and constant coupling of 0 225 second When the right bundle branch was temporarily damaged by means of pressure with the back of a small knife the ventricular complexes of the sinus beats assumed the shape seen in bundle branch block

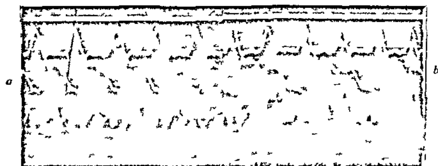


FIG 124 —From an experiment on a dog Tracings from above downward are suspension curves of right auricle and right ventricle electrocardiogram *(ano-oesophageal lead)* *time base 0 02 second* *a* *After injection of* small doses of aconitine No effect on the suspension records or electrocardiogram *b* After faradic stimulation of the right vagus Ventricular bigeminy with extrasystoles of constant shape and accurate coupling From SCHERF 1929a *Z ges exp Med*

(widened QRS complexes *see* Fig 125b) The coupling of the extrasystoles remained unchanged at 0 225 second and this is understandable since the sinus impulse still reaches the left ventricle (in which the extrasystoles originate) without any delay When a few minutes later the right bundle branch had recovered the left bundle branch was completely severed and this resulted in a lengthening of the coupling of the extrasystoles to 0 27 second the shape of the extrasystoles remaining the same (Fig 125c) This lengthening must be attributed to the fact that after the left bundle branch had been cut the sinus impulses could reach the extrasystolic centre only via the longer path of right bundle branch and right ventricle Subsequently the right bundle branch was also severed and complete A V block resulted The idioventricular automatic beats originated in either the right or the left ventricle each being followed by a left ventricular extrasystole as before Again the length of coupling of the extrasystoles depended on the length of the path which the initiating impulse had to traverse in order to reach the extrasystolic centre that is depended on the side at which the preceding automatic idioventricular impulse originated As expected the coupling was shorter if this was in the left ventricle if in the right longer (Fig 125d) Such findings were also as will be shown one of several pieces of evidence supporting the view that extrasystoles originate in a circumscribed focus

FIG 125 —From an experiment on a dog Recording as in the preceding figure *a* Ventricular bigeminy following injection of aconitine *b* After temporary damage to right bundle branch *c* After severing of left bundle branch *d* After severing of both bundles For further explanation see text From SCHERF 1930 *Z ges exp Med*

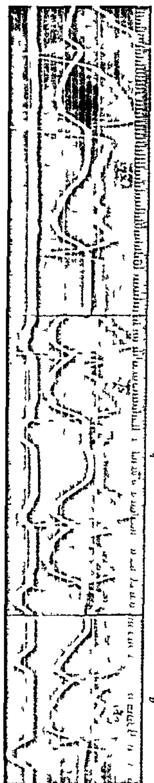


FIG 1 6 —From an experiment on a dog Recording as in the last two preceding figures Gradual lengthening of the coupling caused by quinine From SCHERF and SIEDEK *Z ges exp Med*

The length of coupling of extrasystoles is also affected by certain drugs Regarding extrasystoles produced by aconitine their coupling may increase at the end of a series of extrasystoles just before they disappear (Scherf 1929a) Other drugs having a similar effect on extrasystoles produced in this way are atropine (Scherf 1929b) and quinine (Scherf and Siedek 1935) Fig 126 provides an example of the latter In a dog ventricular bigeminy had been produced by aconitine the extrasystoles having the constant coupling of 0 23 second Following the injection of the unusually large dose of 0 5 gramme of quinine bi sulphate in a 20 per cent solution marked changes occurred in the shape of the extrasystoles and their coupling increased to 0 29 second (not shown) A second injection of the same dose of quinine caused a further lengthening of the coupling to 0 33 second (Fig 126a) and subsequently to 0 36 second (Fig 126b) After a further injection of 0 2 gramme quinine the coupling attained 0 655 second (Fig 126c)

CLINICAL OBSERVATIONS

In clinical experience extrasystoles with constant coupling are far commoner than those with varying one Amongst sixty cases with extrasystoles (fifty-one ventricular nine auricular in origin) followed by a compensatory pause constant coupling was found in 91 6 per cent (Schellong 1924) According to our experience this percentage is probably even higher In this variety of extrasystoles the coupling remains remarkably constant even with pronounced changes in the rate of the S A rhythm (Wenckebach and Winterberg 1927) If the cardiac rate increases considerably as the result of atropine the coupling remains constant (Hering 1904a pulse tracings only) and Samet observed a patient in whom the coupling remained unchanged 0 44-0 46 second during S A rhythm and during an attack of auricular fibrillation Frey (1918) found such variations not to exceed 0 06 second in seventeen out of twenty cases Also in extrasystoles caused by digitalis which are characterized by almost continual changes in shape the coupling was found to vary only by 0 02 second in eleven out of fifteen cases and (with one exception) by not more than 0 03-0 04 second in the remaining ones (Scherf 1931 1932)

If different cases are compared it is found that on the whole the range of coupling of extrasystoles is comparatively small extending from about 0 35 to 0 6 second This is also true for digitalis extrasystoles in fifteen cases in which the coupling was accurately measured it ranged from 0 35 to 0 56 second and seven amongst these showed figures of 0 35–0 45 second (Scherf 1931)

In rare cases this range is considerably exceeded on either end Thus Fig 127 shows auricular fibrillation with extrasystoles occurring with the exceptionally long coupling of 1 12 seconds In such a case a re entry mechanism to account for the extrasystoles is clearly impossible (*see* chapter on Mechanism) The other extreme is illustrated by Fig 128 *obtained from a patient with coronary sclerosis in which extrasystoles are seen with a* coupling of only 0 26 second occurring before the T wave of the preceding beat had been fully inscribed From observations like these it was deduced by some that the extrasystolic stimulus must be a strong one for a critical discussion of this view *see* section on Intensity of Stimulus p 367

If the coupling of ventricular extrasystoles is comparatively long in relation to the rate of the underlying rhythm that is if the extrasystoles occur very late in diastole after the P wave of the subsequent normal beat is fully inscribed they are scarcely premature or not premature at all Fig 129 was obtained from a patient with syphilitic aortitis and coronary stenosis (verified anatomically) The sinus beats show slurred or notched initial ventricular deflections and the final portions are grossly abnormal in all leads lead 3 taken by itself would be suggestive of myocardial infarction in the posterior wall The P R intervals of the sinus beats measure 0 16 second on an average as compared with the 0 14 second of the

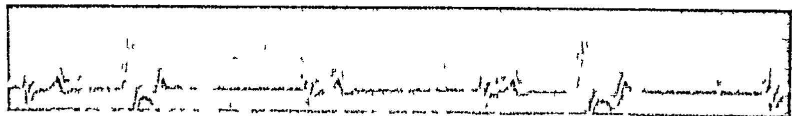


FIG 127.—Auricular fibrillation with ventricular extrasystoles showing the unusually long coupling of 1·12 seconds

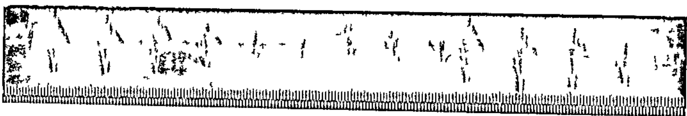


FIG 128.—Series of ventricular extrasystoles the first of which shows the unusually short coupling of 0·26 seconds

extrasystoles Owing to slight variations in the rate of the sinus rhythm the extrasystoles occur so late that in some parts of the tracings the coupling measures as much as the R R intervals between two sinus beats—0 52 second—so that in this case the extrasystoles can hardly be said to be premature Extrasystoles of this timing are formed at a time when the next normal impulse spreads over the ventricles (Calandre 1920) They may easily be confused with sinus beats with aberrant conduction in the ventricles

Periodical Spontaneous Changes in the Length of Coupling

In addition to the common variety of extrasystoles with constant and the infrequent one of ectopic beats occurring with varying coupling periodical spontaneous changes of coupling of extrasystoles are seen in rare instances

One variety is a gradual lengthening of the coupling in successive extrasystoles until one is dropped and the cycle starts anew Three instances of this have been reported In

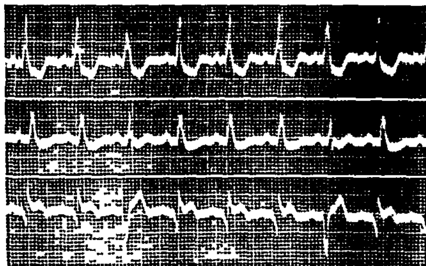


Fig 129—The three standard leads Ventricular extrasystoles occurring so late in diastole that they are not premature

the first published by Zander in 1927 and already referred to in the chapter on Pararrhythmias (p 161) the patient was a man of fifty four with moderate congestive heart failure apparently due to coronary sclerosis The electrocardiogram showed a ventricular bigeminy in which at times the coupling gradually increased from 0 44 to 0 58 second until one extrasystole failed to occur the next sinus beat was followed by an extrasystole with short coupling and the same sequence of events repeated itself Zander explained his observation by the assumption of disturbances of conduction of the normal impulse on its way to the centre of ectopic impulse formation This interpretation was criticized by Goldenberg and Scherf who published in the following year an instance of a similar though more complicated arrhythmia Whereas in Zander s case the arrhythmia was found on only one occasion—subsequent tracings showing either sinus rhythm or ventricular extrasystoles with fixed coupling of 0 48–0 50 second—Goldenberg and Scherf recorded ventricular extrasystoles with periodically changing coupling on numerous occasions Fig 130 top record reproduces one of their tracings The first two b ats are sinus beats the second to fifth

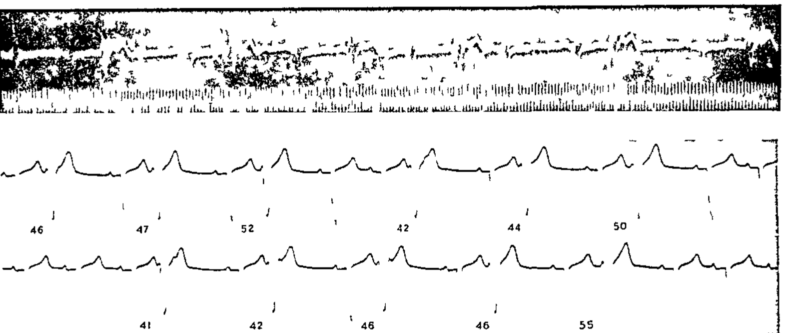


FIG 130.—Two instances of gradual lengthening of the coupling with dropping of extrasystoles. The top record is from GOLDENBERG and SCHERF, *Wien. Arch. inn. Med.* The two strips of the bottom record are continuous; lead V I

sinus beats are each followed by a ventricular extrasystole the coupling of which increases from 0 48 to 0 6 second After the next sinus beat no extrasystole occurs Subsequently the same phenomenon is seen to start again the coupling of the last two extrasystoles in creasing from 0 48 to 0 52 second In this case a coupling of 0 80 was observed on one occasion At other times however the opposite behaviour was recorded namely decrease in length of successive couplings two extrasystoles occurring in succession and having the same shape were also seen whereby the interval between the two ectopic beats was usually shorter than the coupling of the first extrasystole of the group While Goldenberg and Scherf found it impossible to determine the underlying mechanism with any degree of certainty on the ground of their observations in only one such unusual instance they were able to show that their case cannot be explained by assuming disturbances of conduction and that distur bances of impulse formation was a more likely tentative explanation The fact that the shortening of successive couplings tended to be observed at a time when extrasystoles had been absent for some considerable period pointed to some possible analogy with the

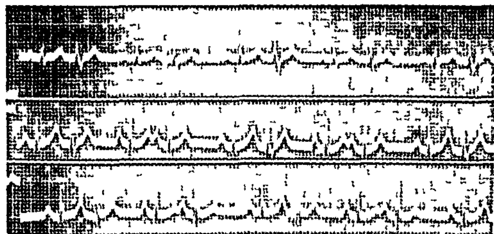


Fig 131 —Auricular bigeminy with alternation in the length of the coupling

rhythm of development namely the gradual quickening of the idioventricular rate after severing the A V bundle in the frog (Gaskell 1883) A somewhat similar case has been observed by Mack and Langendorf

A further example of this rare arrhythmia is illustrated in Fig 130 bottom record ob tained from a forty three year old man with a myocardial infarction in the anterior wall who had received 0 2 g of quinidine sulphate thrice daily The beginning of the tracing shows one ventricular extrasystole after each sinus beat with the coupling gradually increasing from 0 46 to 0 52 second after which two sinus beats occur in succession one extrasystole being dropped The same phenomenon occurred subsequently the coupling gradually increasing from 0 42 to 0 50 after which five sinus beats occurred without any extrasystole The bottom strip shows the same phenomenon namely a gradual increase of the coupling from 0 41 to 0 55 second with subsequent dropping of the premature beats

Another variety of spontaneous periodical changes in the length of couplings is alter nation Fig 131 provides an example recorded in a man of fifty four with emphysema It show continuous *auricular* bigeminy with alternating coupling of the extrasystoles the intervals between the beginning of the P waves of the extrasystoles and that of the preceding QRS complex alternating between 0 28 and about 0 20 second (Owing to the superposition

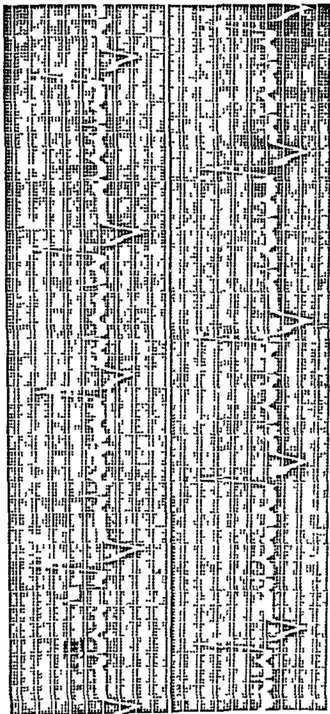


Fig 132 —Lead 3 The two strips are continuous Ventricular extrasystoles after every two sinus beats with alternation in the length of the coupling

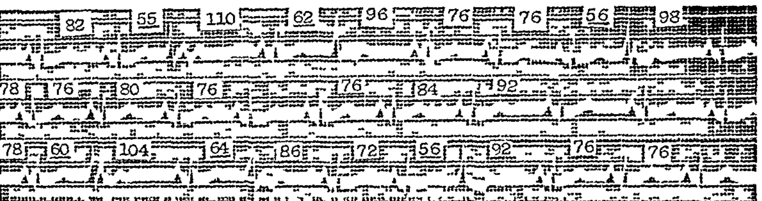


FIG 133 —Lead ? The three strips are continuous Ventricuur extrasystoles with varying coupling also fusion beats without iny evidn e of p rasystol

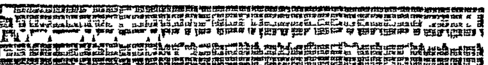


FIG 134 —Lead 2 Sinus (?paroxysmal auricular) tachycardia left bundle bra ch blo k with 2 1 and 3 2 A V b o k From SCHOTT 1951 *Trans med Soc Lond*

of the P waves of alternate extrasystoles upon the T waves of the preceding beats accurate measurement is impossible) The more premature series of extrasystoles shows abnormal *ventricular deflections owing to aberrant intraventricular conduction*

An example of alternating coupling of *ventricular* extrasystoles is provided by Fig 132 recorded in a woman of seventy three a few weeks after an attack of coronary occlusion One ventricular extrasystole occurred after every two sinus beats and their coupling alternated between 0 38–0 40 and 0 56–0 58 second

Occasionally extrasystolic arrhythmias with varying coupling of the ectopic beats and even with fusion beats are recorded in which a parasystolic mechanism cannot be established (Fig *133*)

Bigeminal Heart Action due to Arrhythmias other than Extrasystoles

When a sequence of two heart beats followed by a longer interval is found on auscultation the condition is almost invariably diagnosed as extrasystoles that is one beat of



FIG 135 —All strips lead 2 Partial A V block with idioventricular escaped beats

the dominant rhythm followed by an extrasystole this couple being followed by a post *extrasystolic pause In the majority of cases this clinical diagnosis will be correct* and confirmed if an electrocardiogram is taken But in quite a proportion of such instances the underlying mechanism is different and from a clinical point of view a clear recognition of the arrhythmia is of great importance

Some arrhythmias invariably giving the clinical impression of extrasystoles are fully discussed elsewhere in this book for example dissociation with interference Others too can be distinguished by an electrocardiogram at a glance for instance second grade heart *block in which every third beat is dropped or 2 1 block with occasional or alternating 1 1 conduction (see Fig 134) In others again however detailed analysis of an electro*cardiogram is necessary for an accurate diagnosis to be made Figs 135 136 and 137 provide examples

The tracing reproduced in Fig 135 was obtained in a seventy one year old man with attacks of momentary unsteadiness due to advanced arteriosclerosis The record shows partial heart block after two blocked P waves an automatic ventricular beat (ventricular escape) occurred which was *followed by a conducted S A beat with normal conduction time*

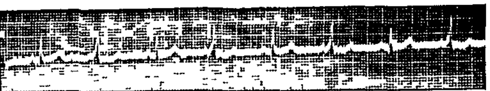


Fig. 136 – Lead I. Pre-excitation syndrome with alternation between normal and abnormal conduction.

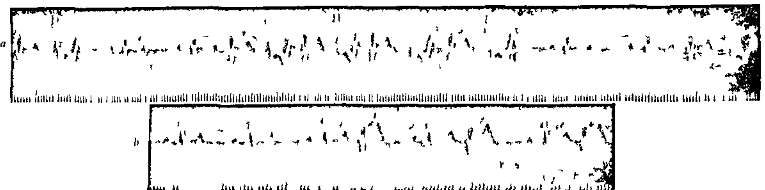


Fig. 137 – From the same patient recorded on different days. Sinus tachycardia with disturbances of A-V and intraventricular conduction simulating ventricular extrasystoles and ventricular tachycardia. For further explanation see text. From SCHERF and KISCH 1953, *Bull. N.Y. med. C.ll.*

(P R 0 16 second) Analysis of longer continuous records supported the interpretation that the conduction of the beats following the idioventricular ones was due to the presence of a supernormal phase of recovery The bigeminal heart action was due to the persistence over long periods of two beats occurring in comparatively quick succession such couples being preceded and succeeded by longer intervals These longer intervals were due to partial heart block and what gave the clinical impression of an extrasystole actually was a conducted beat succeeding an idioventricular one at a short interval (Schott 1949)

Fig 136 at a casual inspection conveys the impression of an extrasystole occurring very late after each normal beat the ventricular complexes of the abnormal beats are slightly premature and as the P waves of these beats are of the same shape as those of the sinus beats and do not occur prematurely such a diagnosis would appear justified that is of the same condition as shown in Fig 129 Closer inspection reveals however that the P R intervals of the abnormal beats are very short (0 08 second as compared with the 0 12 second of the normal ones) and that the upstroke of the R waves of the abnormal beats are grossly slurred whereas the remaining portions of the QRS complexes are of normal shape These features suggest that every second beat represents the Wolff Parkinson White (pre excitation) syndrome which is now commonly attributed to activation of the ventricles through an abnormal pathway often called the bundle of Kent (Holzmann and Scherf 1932 Wolferth and Wood 1933 a short summary of this condition is contained in a paper by Schott 1947) In this present case a diagnosis could not be made with certainty either from the reproduced lead or from the other leads recorded at the time but this was possible by tracings taken after exercise or after inhalation of amyl nitrite whereas extra systoles tend to disappear after the former and to become more numerous after the latter in the present case the rate increased without any other changes in the form of the electro cardiogram

An entirely different mechanism producing bigeminal heart action which again could easily be misinterpreted as due to extrasystoles is shown in Fig 137 In this case bigeminal groups were recorded as well as what appeared to be short series of tachycardia with alter nating form of the QRS complexes (Fig 137a) Measurement reveals however that the underlying rhythm is a rather fast sinus rhythm and that at times every second auricular impulse is blocked During periods of 1 1 conduction grossly abnormal ventricular deflec tions with alternating shape occurred and what gave the impression of extrasystoles actually were supraventricular beats with aberrant intraventricular conduction

Fig 137b recorded from the same patient on a different day can easily be confused with a ventricular bigeminy The first impression is that of sinus rhythm with a ventricular extrasystole following each sinus beat in the second half of the tracing Measurement of the intervals between successive beats reveals at once however that this cannot be the correct explanation since the intervals after the extrasystoles are far shorter than compensatory On the other hand the interval between a normal beat and one having an abnormal ventri cular complex is found to be exactly half of the cycle length between two normal beats while that between the abnormal and the following normal one equals that between two normal complexes The correct interpretation is sinus tachycardia of about 120 with 2 1 block at the beginning of the tracing whereby every second P wave is buried in the T wave of the preceding beat Subsequently the rhythm changed into 3 2 block the first beat of each group shows normal QRS complexes the second is aberrantly conducted in the ventri cles and the third one is blocked (Scherf and Kisch 1939)

In accordance with experimental findings discussed earlier in this chapter lengthening of the coupling of extrasystoles by quinine has also been reported in clinical observations Fig 138 provides an example It was recorded from a patient who was under observation for several years and on numerous occasions had extrasystoles and short attacks of ventri cular tachycardia with alternation of the ventricular complexes On one occasion such an

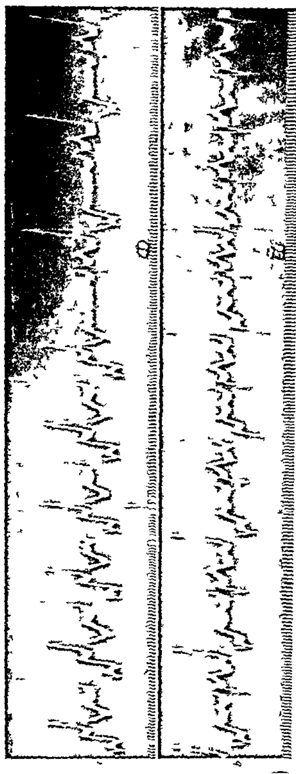


Fig. 118.—Lead 1. Gradual lengthening of the coupling of ventricular extrasystoles caused by an intravenous injection of quinine. For further explanation see text.

attack stopped 27 seconds after the intravenous injection of 0 25 gramme of quinine and was replaced by bigeminal heart action in which one extrasystole with constant shape and increasing coupling followed each sinus beat (Fig 138a) In the first bigeminal group the coupling measures 0 40 second then gradually increases and with the last extrasystole attains 0 56 second — 52 seconds after the beginning of the quinine injection (Fig 138b) About 20 minutes later the effect of quinine had subsided and the former tachycardia with alternating ventricular complexes re appeared (Scherf and Winterberg) Lengthening of the coupling of extrasystoles by quinine was also reported by Scott (1922) Scherf (1924) and McGuire and Rosenberger (1931) It is also occasionally observed after carotid sinus pressure

SUMMAR

Coupling is defined as the time interval between an extrasystole and the beat preceding it

According to their coupling extrasystoles can be divided into two main groups

(1) with accurate (constant fixed) coupling

(2) with varying coupling

The present chapter is confined to the discussion of the above group (1) to which alone in our opinion the term extrasystole in the strict sense of the word should be applied

If one extrasystole with constant coupling follows each beat of the dominant rhythm the resulting arrhythmia is often termed bigeminal heart action or coupled beats While in the majority of observations bigeminal heart action is caused by this mechanism this is by no means invariably the case It is recommended that the term bigeminal heart action be qualified by adding the description of the mechanism responsible for it The historical development of our conceptions of bigeminal heart action is briefly reviewed Reasons are given for the recommendation that the term trigeminus should only be used to describe an arrhythmia in which two extrasystoles follow one beat of the dominant rhythm While extrasystoles with constant coupling are very common in clinical experience they are very difficult to elicit in experimental work The methods known to produce this arrhythmia experimentally and some relevant experimental observations are discussed The length of the coupling of extrasystoles proved to depend *inter alia* on the length of the path which the impulse of the initiating beat had to traverse in order to reach the centre of extrasystolic impulse formation Regarding clinical observations it is pointed out that constant coupling is found in well over 90 per cent of cases with extrasystoles The great constancy of the coupling in the individual case is emphasized It is maintained even if the dominant rhythm shows large variations in rate *On the whole the range of coupling is comparatively small* extending from about 0 35 to about 0 6 second Observations regarding cases with unusually long or short or periodically varying coupling are described Some examples of bigeminal heart action due to arrhythmias other than extrasystoles are given The effect upon the length of coupling of certain drugs as found experimentally and clinically is briefly reviewed

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CHAPTER V

ALTERNANS

INTRODUCTORY REMARKS AND DEFINITION

In considering the phenomenon of alternation its manifestation in the heart as well as in the pulse has to be taken into account Regarding the pulse *pulsus alternans* consists in a regular alternation between a larger and a smaller pulse whereby the smaller pulse occurs either midway between two larger ones or slightly later than midway In such cases the cardiac action is regular normal S A rhythm, and the alternation in the strength of the pulse is due not to any arrhythmia or allorhythmia but to an alternating change in the force of the cardiac contraction According to Kisch (1932) Cardiac alternans may be defined as a regular alternation in the bio-energetic processes in the heart occurring in two consecutive beats and not being due to the regular alternation in the time sequence of the individual contractions (our translation) With certain reservations which Kisch pointed out Gravier s (1914) definition can be said to state the essence of the phenomenon as alternance de force des contractions sans altération de leur rythme

It could thus be argued that a discussion of the alternating pulse is out of place in a book devoted to certain arrhythmias We have included it for two reasons

The first is historical As is pointed out in the historical remarks and in the chapter on Coupling the alternating pulse was first described by Traube who clearly recognized its characteristics including the correct time relations between large and small pulses In spite of the accuracy of his observations he considered it as one variety of the bigeminal pulse and thereby created a confusion affecting diagnosis as well as prognosis which was to obscure the true significance of extrasystolic bigeminy and alternation for a long time to come This may well be one reason why a discussion of the *pulsus alternans* was included in the classical monographs of Lewis (1925) and of Wenckebach and Winterberg (1927) A second and more important reason for our including this phenomenon is the fact that extra systoles greatly enhance alternation of the pulse

It has been pointed out above that in instances of *pulsus alternans* the rhythm of the heart is normal regular S A rhythm While this is correct for the vast majority of cases it should be qualified by adding that some rare exceptions exist in which bigeminal rhythm due to extrasystoles occurring very late in diastole (*see* below) and certain varieties of heart block occasionally give rise to *pulsus alternans* (Lewis 1925)

DIAGNOSIS

This is often made by the palpating finger particularly with the patient s arm slightly raised and the brachial artery slightly compressed The most sensitive method to discover even slight degrees of alternation is the auscultatory method of taking the blood pressure on slowly decompressing the cuff the smaller pulses are at first not heard at all and subsequently over a range of pressures varying in different patients the alternation in the intensity of the arterial sounds is very obvious In rare cases in which the weaker pulses are very small only every other pulse is felt at the wrist

The differentiation between *pulsus alternans* and *pulsus bigeminus* is discussed below in this chapter

INCIDENCE

The phenomenon is common if searched for (Gravier, Poumailloux) It was found in seventy one out of three hundred pulse tracings recorded from patients with cardio vascular disease and in 33 per cent of patients with congestive heart failure (White)

EXPERIMENTAL INVESTIGATIONS

Experimentally alternating pulse is readily observed with increased arterial resistance (Straub) fatigue (Hofmann) or after coronary ligation (Kisch 1921) Various substances are known to precipitate it for example digitalis aconitine (Cushny) and veratrine

EXTRASYSTOLES AND ALTERNATING PULSE

The precipitation by extrasystoles of an alternating pulse has been extensively studied (Gaskell Langendorff Woodworth Volhard Rihl (1906a b) Mackenzie Tabora) In the series of seventy one cases of White mentioned above alternating pulse was seen only after

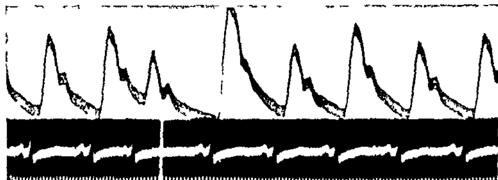


FIG 139 —Radial pulse tracing electrocardiogram and time base (0 04 second) Pulsus alternans precipitated by an auricular extrasystole From SCHERF and BOYD *Cardiovascular Diseases* Heinemann London

extrasystoles in fifty five instances Sometimes alternation precipitated by an extrasystole may last for as many as forty pulses According to some authors an alternating pulse may not appear immediately but only after a few pulses following an extrasystole The beginning of alternation just before an extrasystole as reported by Windle (1911) and by Rosenthal seems to us a coincidence A diminished degree of alternation following an extrasystole (Rihl 1906b) or even its disappearance (Muskens Windle 1910) were occasionally seen These are exceptions to the common effect of extrasystoles enhancing or provoking alter nation Whether or not extrasystoles have this effect depends not only on the condition of the heart but also on its rate and on the number of extrasystoles In some patients with frequent extrasystoles a continual alternans seems to exist because the extrasystoles main tain it for long periods In cases showing alternation during regular normal sinus rhythm extrasystoles accentuate the alternation

Arrhythmias other than extrasystoles may have a similar effect for instance dropped beats (Hering 1908) It seems that it is not the extracontraction but the irregularity of rhythm which elicits the alternation

Fig 139 was obtained from a patient with coronary sclerosis and auricular extrasystoles The abnormal T waves indicate myocardial damage In the radial pulse tracing the first post-extrasystolic pulse is very high The next pulse is smaller and regular alternation in the height of the pulse waves can be recognized in the subsequent beats

Just as in Fig 139 the first post extrasystolic pulse wave is always higher whatever the height of the last pulse preceding the extrasystole may have been (*see also* p 363) For this reason an extrasystole changes the sequence of alternation in some cases (The only dissident report of a weaker first post extrasystolic pulse (Fredericq 1912) can be disregarded since in the absence of an electrocardiogram the nature of the post extrasystolic beat particularly its mode of spread cannot be determined)

AURICULAR ALTERNANS

Auricular alternation manifests itself by alternation in the height of the (auricular) *a* waves in the phlebogram Such instances were described by Lewis (1911) and by Pezzi and Donzelot (1913) Doubts regarding the diagnosis were expressed by Gravier but Pezzi and Donzelot reported in 1921 an observation in a patient with nephritis and azotemia in whom auricular alternans followed auricular but not ventricular extrasystoles

CARDIAC PHENOMENA

Pulsus alternans is often associated with cardiac alternans In such cases alternation of the force of cardiac contraction can be felt on palpation or recorded in a (mechanical) cardiogram Also the second aortic sound may alternate in intensity and the alternating strength of contractions can be recorded in a kymogram

As distinct from such alternation in the dynamic force of the cardiac contraction *electrical alternans* is defined as alternation in height or form of some or of all waves of the ventricular complex of the electrocardiogram Such electrical alternans is often found in otherwise normal people during an attack of paroxysmal tachycardia in rare instances the P waves show electrical alternans (*see* Fig 140) Disturbances of conduction are another frequent cause Recently the various mechanisms underlying electrical alternation were experimentally studied and classified on electrophysiological grounds by Lepeschkin What *is relevant in the context of this book is that the electrical alternans may or may not be* associated with mechanical alternation

DIFFERENTIATION BETWEEN PULSUS BIGEMINUS AND PULSUS ALTERNANS

In the great majority of cases this differentiation can easily be made by an electrocardiogram or by simultaneous mechanical records of radial pulse (or preferably apical cardiogram) and jugular pulse By such records it is possible without great difficulties to recognize extrasystoles and thereby to ascertain whether the sequence of larger and smaller pulses is due to premature beats or associated with normal rhythm

The diagnosis from radial pulse tracings alone is possible in a considerable proportion of cases but often fraught with difficulties The main diagnostic criterion is that in the average case the small pulse is premature in bigeminal rhythm due to extrasystoles whereas it occurs with some delay in *pulsus alternans* The reason for this delay is the lengthening of the presphygmic period This is due to the delay in the opening of the aortic valves by the weaker contraction which has to overcome the higher diastolic pressure in the aorta (and the whole arterial system) resulting from the preceding stronger contraction (Volhard) It might thus appear that the difference in these two pulse forms should make it possible easily to diagnose the underlying mechanism The conditions are however greatly complicated by the fact that in extrasystoles too the presphygmic period is lengthened Measured as the time interval between the beginning of systole as recorded in the mechanical cardiogram and the beginning of the upstroke in the radial pulse tracing it may amount to as much as 0 04 second (Hering 1902) This is largely due to the altered haemodynamics in ectopic beats in particular the lengthening of systole (*see* p 355) Therefore if extrasystoles occur late in diastole their pulse may well be not premature in the radial tracing

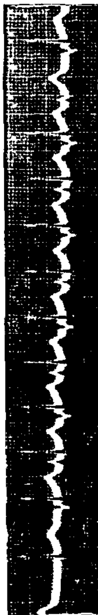


FIG 140 —From a healthy woman of 35 Electrical alternans of the P waves during an attack of paroxysmal tachycardia

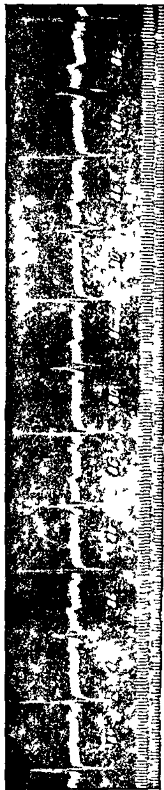


FIG 141 —Ventricular extrasystoles occurring late in diastole simulating electrical alternans Time base 0 04 second

Fig 141 provides an example of this kind of extrasystoles It shows regular alternation between normal and slightly abnormal ventricular complexes whereby the outstanding difference is the alternation in the height of the various waves of the ventricular complexes Since both types are always preceded by P waves at normal intervals casual inspection would indicate the presence of sinus rhythm with electrical alternans Measurement reveals however that the smaller and abnormally looking complexes occur after an interval of 0 80 while the following cycle length measures 0 86 second The abnormal beats are therefore ventricular extrasystoles occurring very late in diastole at a time when the next normal sinus beat was about to be due That this diagnosis is the correct one could be proved by other tracings of this patient in which the extrasystoles occurred earlier in diastole and the diagnosis could thus easily be made It is obvious that in such instances a radial pulse tracing would show the smaller pulse of the extrasystole to occur so late that the time relations would be indistinguishable from those produced by alternation with regular sinus rhythm (*See also* Fig 129 on p 199)

Moreover a slight delay in the small pulse due to alternans may easily be missed in the radial tracing

If follows that the differential diagnosis from radial tracings alone between *pulsus bigeminus* due to extrasystoles and *pulsus alternans* may be extremely difficult not infrequently it is impossible In view of the entirely different clinical significance of these two phenomena the importance of a correct diagnosis needs no emphasizing In some instances the result of exercise is helpful whereas after exercise extrasystoles tend to disappear temporarily alternation usually becomes more pronounced

DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF PULSUS ALTERNANS

The essential clinical significance of *pulsus alternans* is that as a rule it indicates myocardial damage When found with a slow heart rate this is invariably the case whereas with higher rates in particular 120 and more it has sometimes been encountered in individuals without any other sign of cardiac disease and it has also been observed during paroxysmal tachycardia in otherwise healthy subjects According to Wenckebach and Winterberg alternation for a few beats after an extrasystole likewise occurs in healthy people It may change from minute to minute and may appear and disappear without any known cause (Lewis 1925)

In patients with hypertension alternans often is an early sign of heart failure

The prognostic significance depends on the underlying condition which gave rise to the *pulsus alternans* Thus in myocarditis or toxic myocardial damage in diphtheria alternation may disappear concurrently with the recovery of the myocardium The same is also found after myocardial infarction In such cases the temporary occurrence of *pulsus alternans* cannot be said to have any lasting prognostic significance But even persisting alternating pulse though in most cases a sign of serious prognosis need not indicate the imminent breakdown of the circulation in every case Thus one patient with *pulsus alternans* was observed for six years (Tabora) and another for five years (Swildens) the latter was under observation by one of us for two additional years when alternation was invariably present

UNDERLYING MECHANISM

Starting with Gaskell s work a difference in the excitability of the individual myocardial fibres was widely regarded as the cause of alternation Originally it was assumed that the large pulse is due to the contraction of all the ventricular fibres whereas the smaller one was thought to be produced by the contraction of only a fraction of such fibres This view was found not to explain all observations and Mines explanation became more widely accepted According to him alternation is due to the alternating contraction of a greater and of a

smaller number of myocardial fibres according to the formula $V\ V_1\ \ V\ V_2\ \ V\ V_1$ etc whereby V stands for all the ventricular myocardial fibres V_1 and V_2 for a smaller and a larger fraction respectively of fibres belonging to both ventricles One of many variations of this view is that of Wenckebach (1901) and of Wenckebach and Winterberg who laid the emphasis on small alternating differences in filling Any theory to explain this phenomenon has to include the observation that alternation of contraction has been observed in isolated muscle strips (Weekers Fredericq 1913) For a discussion of the various theories the reader is referred to Kisch s monograph (1932)

SUMMARY

In accordance with Kisch cardiac alternans is defined as a regular alternation in the bio energetic processes in the heart occurring in two consecutive beats and not being due to the regular alternation in the time sequence of the individual contractions (our translation) It was included in this book for two reasons first from a historical point of view because of the confusion between *pulsus alternans* and *pulsus bigeminus* due to extrasystoles with its consequent effect on the ideas of the prognostic significance of these conditions second because extrasystoles greatly enhance alternation of the pulse The diagnosis and incidence of *pulsus alternans* are discussed and some relevant experimental investigations briefly reviewed The relationship between extrasystoles and *pulsus alternans* is discussed in some detail and brief reference made to auricular alternans The cardiac phenomena of mechanical and electrical alternation are described The differentiation between *pulsus alternans* and *pulsus bigeminus* is discussed in some detail with special reference to difficulties encountered in cases of extrasystoles occurring late in diastole The essential diagnostic and prognostic significance of *pulsus alternans* consists in its being an indication of myocardial damage and in patients with hypertension it often is an early sign of heart failure Instances are discussed in which temporary and even persisting alternating pulse may not be a sign of grave omen As far as the underlying mechanism is concerned Mines explanation has become more widely accepted according to which the phenomenon is due to the alternating contraction of a greater and of a smaller number of myocardial fibres belonging to both ventricles

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CHAPTER VI

FLUTTER FIBRILLATION AND PAROXYSMAL TACHYCARDIA

FLUTTER AND FIBRILLATION

General Remarks applicable to Auricular and Ventricular Varieties

In this section we propose to demonstrate that the mechanism underlying flutter and fibrillation both auricular and ventricular is far more akin to that of ectopic beats and extrasystoles than commonly assumed until quite recently in particular regarding the auricular variety A discussion of the *nature* of these arrhythmias is therefore pertinent in a book devoted to extrasystoles and allied arrhythmias We do not propose however to include a description of the electrocardiographic appearances or clinical aspects of these conditions as they constitute separate and well known entities which are fully discussed in the cardiological textbooks Only one familiar clinical observation may parenthetically be mentioned in order to illustrate the close clinical relationship between extrasystoles and flutter and fibrillation namely that auricular extrasystoles particularly the multiform variety often are precursors of auricular fibrillation and the same holds good for multiple or multiform ventricular extrasystoles regarding ventricular fibrillation

Fibrillation was discovered much earlier than flutter namely ventricular fibrillation by Hoffa and Ludwig in 1850 (pp 129 *seq*) and that of the auricles by Vulpian in 1874 Auricular fibrillation in man was established in 1909 by Lewis and by Rothberger and Winterberg Auricular flutter was first described experimentally by McWilliam in 1887 and in man by Jolly and Ritchie in 1911 It is thus understandable that the earlier theories dealt only with fibrillation The close relationship between fibrillation and flutter was emphasized by Rothberger and Winterberg in 1914

Of the various theories put forward to explain these disturbances of rhythm three may be mentioned as having attracted most attention

1 Theories based on the assumption of dissociated action of various groups of muscle fibres (Kronecker) The first indication of this view can already be found in the description of the discoverers of fibrillation (Hoffa and Ludwig 1850) in which they say (regarding the entirely irregular rapid and weak movements of the heart on strong electrical stimulation)

The irregularity of these movements is due to the fact that the individual anatomical elements lose their relationship to one another and cease to contract simultaneously (our translation)

Subsequently the emphasis shifted to the nature of the impulses and their formation which produced such contractions

2 Theory of tachysystoly According to this fibrillation is due to the rapid formation of stimuli in ectopic centres This hypothesis was based on Engelmann s view (1896) that in certain experimental conditions automatic stimuli arise in various groups of myocardial fibres which interfere with one another affecting contractility and conduction with the result that various kinds of arrhythmias are observed of which he mentioned fibrillation

Wuhlen and *delirium cordis* Hering (1900) considered ventricular fibrillation to represent the highest degree of enhanced ectopic impulse formation Winterberg (1907) attributed this condition to impulses originating in many centres and the condition as a whole was aptly termed functional fragmentation by Lewis who also stressed the pathological

nature of the impulses which at that time he considered similar to or identical with those of extrasystoles (Lewis 1913)

This theory of polytopic stimulus formation seemed supported by the observation that if a fibrillating ventricle was divided into several parts fibrillation did not stop but the fragments continued to fibrillate (Kronecker Hering 1917 p 22)

In further studies on the mechanism of fibrillation and flutter Rothberger and Winterberg (1914 1916) pointed out that fibrillation may be found in the presence of a co ordinated cardiac action and put forward the view that rapid stimulus formation in only *one* centre may suffice to produce fibrillation and flutter they also stressed the close relationship between these two arrhythmias This view of a unifocal origin of ventricular fibrillation and flutter emphasized the fundamental similarity between the mode of origin of these two arrhythmias on the one hand and that of extrasystoles on the other

Whereas none of the authors mentioned nor others who held similar views (for example Kisch) specified the site of the presumed ectopic impulse formation Haberlandt located it in the A V region

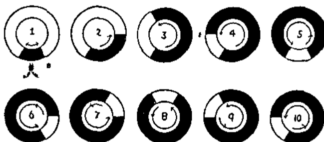


FIG 142 —A diagram to illustrate the establishment of circus movement in a ring of muscle The ring is stimulated in its lower quadrant and the wave spreads to A and B past A it fails to go but it continues on the right until it reaches E (1 to 4) At this instant recovery begins at A and as the crest advances beyond E refractoriness retreats in the lower quadrant (5) The advance and the retreat now occur at equal rates and the crest continues to circulate in the ring at a fixed distance from the wake (6–10) From LEWIS (1925) *The Mechanism and Graphic Registration of the Heart Beat* 3rd ed Shaw & Sons London

Another objection against the theory of polytopic stimulus formation was based on the observation that fibrillation often stops suddenly without any intermediate changes in the electrocardiogram If many centres were active it was argued their sudden simultaneous cessation of producing stimuli would be difficult to understand (Kisch) This argument loses much of its force if it is realized that in fibrillation impulses originating in one centre and in many centres may yield identical electrocardiograms (Scherf 1951) The successive termination of stimulus formation in the centres would be unrecognizable in the record and only if the last centre stops would the sudden change in the electrocardiogram take place

These theories receded into the background when the view became generally accepted that fibrillation and flutter were due to a circus movement

3 Theory of circus movement This is based on the fundamental experimental work of Mayer Mines and Garrey who demonstrated that in certain experimental conditions one stimulus applied to a muscle ring produces an excitation wave which may continue to circulate and excite for considerable periods sometimes amounting to hours Mines and Garrey considered the possibility that this observation may explain the mechanism of flutter and fibrillation but its widespread acceptance as an explanation for auricular flutter and fibrillation is due to the brilliant work of Lewis and his collaborators

The principle of the theory of circus movement is too well known to justify any further discussion Fig 142 may serve to summarize the mechanism assumed to underlie this phenomenon (*see also* p 120)

Lewis and his collaborators attempted to prove in two ways that fibrillation and flutter are due to a circus movement 1 Experimentally by determining the order of activation of the auricles during flutter and fibrillation by means of direct leads By this method they found that the main (mother) excitation wave circulated in the auricles through a path consisting of the *taenia terminalis* and around the large veins Centrifugal daughter waves activated the auricular portions outside the range of the main wave It was however not possible to investigate the whole of this presumed path since the posterior part of the left auricle could not be fully explored 2 Clinically by calculating the movements of the electrical axis of auricular activation in a case of auricular flutter by means of simultaneous records obtained with three special leads It was found that this axis rotated through a full circle of 360 around the great veins (Lewis Drury and Iliescu)

From these investigations Lewis and his co workers concluded that *auricular* flutter and fibrillation are due to a circus movement In flutter a single circus movement was thought to exist which travelled on a path repeated with much accuracy from cycle to cycle (Lewis 1925 p 340) In fibrillation a single circus movement again was assumed but the path followed is uneven in its detail it constantly alters and sometimes though for brief periods the path changes more grossly but in general the same broad path is used over and over again (*Ibid* p 341)

Regarding *ventricular* fibrillation Lewis postulated a similar mechanism but pointed out that there was no direct evidence of a wave circulating in the ventricles Garrey (1924) on the other hand thought that in ventricular fibrillation circulating waves may occur at any place in the cardiac chambers owing to areas of diminished conductivity which prevent the excitation wave from pursuing its normal path (*see also* below p 230)

The further discussion can with advantage be divided into that of auricular and of ventricular fibrillation and flutter

Auricular Flutter and Fibrillation

One of the reasons for the ready and widespread acceptance of Lewis s conception of auricular fibrillation and flutter was that the theory of circus movement afforded a plausible explanation of the conversion of flutter into fibrillation by vagal stimulation (Rothberger and Winterberg 1914) It was known that vagal stimulation shortens the refractory period of the auricles but Rothberger and Winterberg hesitated to assume that it also increases the rate of impulse formation The circus movement theory seemed to explain this effect upon flutter of vagal stimulation in a most satisfactory manner The shortening of the refractory period abolished more quickly the islands of refractoriness of tissue—caused by the excitations following in quick succession—and thereby made it possible for the circulating wave to use shorter because less circuitous paths that is stimulate the auricles at the faster rate of fibrillation as compared with the slower one of flutter This increase in rate of auricular stimulation as a result of shortening of the refractory phase can however be explained in a different way If it is assumed that the stimulus is continuous the rate of response will depend on the length of the refractory phase and therefore will increase if the refractory period is shortened by vagal stimulation (*See also* below (9) rapid re excitation) The stimulating effect upon ectopic impulse formation of acetylcholine (*q v* p 328) is relevant in this context If a rhythmic stimulus is envisaged shortening of the refractory phase may also cause a more rapid stimulus formation and timuli would become supra threshold at an earlier stage

Objections against the circus movement theory were however raised at a very early

stage particularly by Rothberger (1922) which in view of recent developments necessitate a more detailed discussion The most important ones are

1 As already indicated above in determining experimentally the movements of the electrical axis in flutter Lewis could not examine the whole path since the posterior portions of the left auricle were inaccessible to such investigation Rothberger pointed out that Lewis s assumption of the circulating wave s traversing that part of the circle was based solely on calculation

2 The above argument of Rothberger gains in importance if it is realized that special investigations have failed to show the presence of muscle bundles in some portions of the left auricle (particularly near the orifices of the pulmonary veins) which would be necessary to complete the circular path assumed by Lewis to be traversed by the circulating wave (Rothberger 1931)

3 The theory of circus movement assumed that it continues as long as there is a gap of excitable tissue between the head and tail of the circulating wave It was therefore emphasized as an important point in favour of this theory that one strong electrical shock abolished auricular fibrillation this being explained by the abolition of the gap by the shock If this reasoning were correct every electrical stimulus strong enough to excite the whole auricle should always terminate immediately auricular fibrillation in this way as a gap would have to be assumed to be continually present this however is not the case Mines wrote already in 1913 *This —that is a single shock— if timed properly instantly arrested both chambers* (our italics)

4 According to Lewis in the dog s heart during auricular fibrillation and flutter the main wave invariably travels up or down the sinus node It would therefore have to be expected that interruption of this path by broad ligatures applied round the *taenia terminalis* should terminate auricular flutter In sixteen out of seventeen such experiments flutter persisted without any change in the shape of the F waves in the electrocardiogram This observation is incompatible with a circus movement through paths postulated by Lewis (Scherf 1928)

5 If flutter is experimentally produced by faradic stimulation the flutter waves usually have the same shape as the P waves of the sinus beats Moreover if by certain experimental interferences changes in the shape of the P waves of the sinus beats were produced subsequent flutter showed F waves of the same altered shape These observations suggest that flutter originated in the same area in which the preceding (or succeeding) slower rhythm arose (which was either sinus or A V rhythm) and are incompatible with Lewis s assumption of a circus movement (Scherf 1928)

6 The last observation (5) also tends to strengthen an objection which Rothberger had put forward against the validity of Lewis s conclusions from his clinical observations As stated above by calculating the movements of the axis of auricular activation in a patient with auricular flutter Lewis Drury and Iliescu found a rotation through a full circle Rothberger s objection to this was that the recorded waves on which this calculation was based were most unlikely to have been due to the excitation of the tissue in the path of the circulating wave involving thin muscle bundles but were due to the activation of the mass of auricular muscle Rothberger contended therefore that it was not permissible to draw any conclusions about the course of a mother wave from deflections which are due to the whole of the auricular musculature The findings listed above (5) emphasize the validity of Rothberger s argument since in Scherf s experiments the changes in the P waves were effected by interferences applied at a considerable distance from the path of the mother wave as postulated by Lewis

7 It was found in the dog s auricle by Andrus Carter and Wheeler that an electrical stimulus introduced during vagal stimulation shortly after the end of the refractory period could produce auricular fibrillation This was observed also if the stimulus was applied

well out on the auricular appendix As there was no measurable gap between the stimulus and the beginning of the re entrant rhythm these authors concluded that the excitation arose at the site of stimulation and not in a ring of muscle at the base of the auricle This observation is thus also not in accordance with Lewis s theory and is far better explained by repetitive impulse formation at the site of stimulation

8 In some cases of disorders of auricular rhythm a sudden marked increase in the rate has been reported (flutter Cookson and Clark Kennedy Parsonnet and Parent A V tachycardia Rosenbluth and Winterberg auricular paroxysmal tachycardia Camp and Scherf) Of these we do not concur with the interpretation of the records given by Cookson and Clark Kennedy and Parsonnet and Parent Even if these were instances of a sudden doubling of the flutter rate which we do not consider the published tracings demonstrate in any way convincingly we could not accept the explanation that this is due to the excitation wave s suddenly pursuing a path of half its former length this seems an entirely arbitrary assumption put forward to explain the records as interpreted by these authors In such cases the assumption of rapid stimulus formation with a former 2 1 response changing into a 1 1 response seems far preferable as postulated in the case published by Camp and Scherf

9 It has been observed that vagal stimulation during auricular fibrillation may suddenly increase the rate of stimulation to 2 000–3 000 per minute Lewis called this phenomenon rapid re excitation and explained it by assuming that the circulating wave pursues a path with a very small diameter The path around the large veins is much too long to account for such high rates of re excitation No explanation has been offered why and how a much shorter path is suddenly traversed by the excitation Since it is known that faradic stimulation of the vagus may shorten the refractory phase of auricular tissue to one fifth of its former value these very high rates of excitation can be explained by a fivefold increase in the rate of response of the auricle to a continuous stimulus or a fivefold increase in the rate of rhythmical stimulus formation

These observations have been discussed in some detail in order to demonstrate that starting almost immediately with the inception of the theory of circus movement as accounting for the mechanism of flutter and fibrillation weighty objections had been put forward against it by the early thirties Some additional work of that period expressing similar doubts may be found in the reviews by Winterberg (1926) and by Rothberger (1931 p 707) De Boer s views are also shortly discussed by Rothberger (1923) and in the chapter on Mechanism (p 483)

In recent years series of experiments carried out by Scherf and his collaborators since 1946 with new techniques have yielded results which tend to prove that auricular fibrillation and flutter are due to the rapid stimulus formation in one centre the former in certain conditions in several centres Their observations are all incompatible with the circus movement theory which they can be considered to have disproved in the conditions of their experiments

In these investigations a method was employed to produce auricular arrhythmias which was described by Langendorff almost seventy years ago namely the topical application of chemical compounds to the cardiac surface Of these aconitine was used in the great majority of these studies namely application of a few crystals of pure aconitine to a small area at various points of the auricular surface or by sub epicardial injection of 0 05 cc of a 0 05 per cent solution of aconitine *

By this method it was possible with great constancy to precipitate within one minute a regular auricular tachycardia with a rate of about 300 per minute Cooling the site of

* This method of *topical* application of aconitine is distin t from the *systemic* use by intravenous injection of this substance which was widely used in previous experiments of Scherf and co-workers a considerable time ago see chapter on N rvous System p 255

application of the drug or separating it from the rest of the auricle by means of a clamp immediately abolished the tachycardia which re appeared within 1–3 seconds after cooling was discontinued or the clamp removed From these observations it was concluded that the ectopic auricular tachycardia originated in one focus namely the site of application of aconitine Vagal stimulation during auricular tachycardia usually increased its rate but auricular fibrillation was never observed in that series of experiments Such arrhythmias presented some features suggestive of flutter but essential paroxysmal tachycardia could not entirely be ruled out at that time (Scherf 1947) It was however pointed out by the author already at the time that the results are not compatible with Lewis s circus movement theory if this tachycardia proved to be flutter Similar arguments were put forward by Scherf in 1948 These studies were extended by Scherf Romano and Terranova (1948) with the one important modification that aconitine was injected into the head of the sinus node In this series as distinct from the former one it was found that auricular fibrillation occurred spontaneously or was easily induced by vagal stimulation Here again cooling immediately abolished the arrhythmia which re appeared when cooling was stopped The ready transition in these experiments of the auricular ectopic arrhythmia into auricular fibrillation either spontaneously or as a result of vagal stimulation as well as the observation that vagal stimulation never abolished it made it possible to determine the auricular arrhythmia as auricular flutter as distinct from auricular paroxysmal tachycardia The result of these experiments could only be explained by assuming that auricular flutter and fibrillation are initiated by rapid impulse formation in a single center (p 250)

This view was supported by further experiments on the effect upon such arrhythmias produced by the topical application of aconitine of stretching auricular muscle or pressure on the site of drug application these measures produced an increase in rate or conversion of flutter into fibrillation or resulted in the re appearance of flutter or fibrillation if this had subsided prior to these interferences (Scherf Scharf and Goklen) It is known that stretching and pressure cause a more rapid depolarization and increase the rate of impulse formation but there is no reason to assume that they have any effect on conduction This observation could hardly be understood if a circus movement is assumed for it would be difficult to explain how pressure exerted with a thin probe on an area with a diameter of 2–3 mm could produce an increase in rate of conduction of a circulating wave An increased rate of impulse formation on the other hand is known to occur in nerves as a result of pressure and stretch in the whole heart of frogs stretch was found to be associated with a negative potential (Rothschuh) which enhances spontaneous impulse formation (*see also* p 501) The inference from these experiments again was that such ectopic arrhythmias originate in a focus and are not due to a circus movement (Incidentally these experiments may also have a bearing on the clinical observation that in certain clinical conditions exertion may precipitate auricular arrhythmias *see* section on Exercise p 413)

Faradic stimulation of the cardiac sympathetic nerves was found to increase the rate of ectopic auricular tachycardias elicited by the topical application of aconitine to the sinus node or to various portions of the auricles This effect was abolished by atropinization and attributed to increase in vagal tone by way of reflex (Scherf 1949)

The view that such arrhythmias produced by aconitine originated in a circumscribed focus and were not due to a circus movement was strongly supported by further observations on the effect upon the onset or recurrence of the aconitine tachycardia of simultaneous cooling of the site of application of the drug and faradic stimulation of the left vagus This abolished the flutter which after cooling and vagal stimulation had been discontinued gradually re appeared The constant shape of the P waves in re appearing flutter of gradually increasing rate and the frequently observed longer intervals between successive P waves made it possible to exclude a circus movement with even greater certainty (Scherf

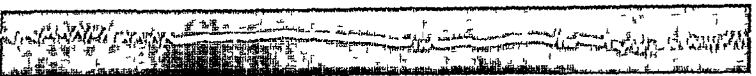


Fig 143.—From an experiment on a dog The beginning of the record shows auricular fibrillation elicited by the sub epicardial injection of aconitine into the head of the sinus node Abolition of the arrhythmia by cooling the site of application of the drug (middle of the record) with subsequent re-appearance of fibrillation when cooling was stopped (end of the tracing)

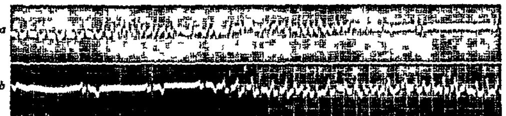


Fig 144.—From an experiment on a dog (25th March 1947) *a* Stretching of the wall of the auricle increased the rate of auricular flutter and converted it into fibrillation which was subsequently abolished by cooling the site of application of aconitine *b* Re appearance of flutter when cooling was discontinued

and Terranova 1949) These experiments also showed that by cautious cooling auricular fibrillation could be converted into flutter and auricular extrasystoles

Some of these observations are illustrated in Figs 143–146

The beginning of Fig 143 shows auricular fibrillation which had been precipitated in a dog by the sub epicardial injection of aconitine into the area of the head of the sinus node The remaining part of the figure shows the immediate cessation of fibrillation and restoration of sinus rhythm on cooling the site of aconitine application, and the subsequent re appearance of fibrillation when cooling was discontinued

Fig 144a shows in its beginning auricular flutter precipitated by aconitine Stretching of the wall of the auricle immediately increased its rate to over 600 per minute and converted it into fibrillation This was promptly abolished by cooling the site of aconitine application After cooling was discontinued flutter re appeared (Fig 144b)

Fig 145 was obtained from a dog in whom the topical application of aconitine had precipitated auricular flutter which subsequently disappeared (beginning of the tracing) Stretching of the auricle caused flutter to re appear for the duration of the stretching

Fig 146 shows auricular flutter with alternation in the duration of auricular diastole during vagal stimulation Auricular flutter was produced by aconitine and before vagal stimulation the flutter rate was 270 every stimulus being conducted to the ventricles During stimulation of the left vagus complete A V block ensued and the reproduced alternation in cycle length was observed The long intervals between every second auricular wave exclude the existence of a circus movement its long absence amounting up to 0 45 second and subsequent re appearance would be inexplicable

It could be argued that cooling of the site of aconitine application could abolish flutter also if this arrhythmia were due to a circus movement But the immediate re appearance of flutter showing the same shape of the F waves as before its temporary suppression constitutes strong evidence in favour of its origin in a circumscribed focus by way of rapid stimulus formation It would seem extremely improbable that a circus movement should immediately be resumed through identical paths after such temporary suppression there are no grounds for the assumption that a circus movement could start again of its own accord in this way after it was interrupted And if as in some experiments described above such flutter waves were separated by longer intervals a circus movement becomes an impossibility

With *focal* application of aconitine the presence of only one focus of stimulus formation is easily understood It had to be expected that whenever auricular fibrillation occurred after aconitine has been spilled over the auricle or after its intravenous administration more than one centre of stimulus formation would be active and that in such circumstances cooling of one focus or even of the whole sinus node would not terminate auricular fibrillation Thus was actually found to be the case (Scherf *et al* 1948 1950a)

Furthermore observations made in auricular fibrillation produced by the topical application of aconitine cannot unreservedly be applied to seemingly identical disorders of auricular rhythm produced by other means Thus auricular fibrillation precipitated by electrical stimulation of or topical application of acetylcholine to the auricles is not stopped by cooling the site of stimulation or of application of the drug but in twenty four out of twenty seven experiments could be terminated by the simultaneous cooling of the sinus and A V nodes (Scherf *et al* 1950a) Similar observations were made with the topical application of veratrine and the intravenous one of aconitine and pilocarpine (Scherf *et al* 1950a Scherf 1951) The results obtained in arrhythmias produced by electrical stimulation or topical application of drugs other than aconitine indicated that in such conditions more than one centre of rapid impulse formation is active and that auricular fibrillation cannot be considered to be due to one uniform mechanism in all cases Evidence will be discussed below in the section on ventricular fibrillation that rapid impulse formation in one ectopic centre may awaken that in others But all these investigations point to rapid

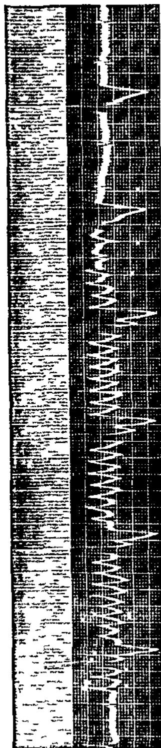


Fig 145.—From an experiment on a dog Re appearance of auricular flutter due to stretching the auricle Complete A V block is present owing to the severing of both bundle branches For further explanation see text

impulse formation in one centre as the mechanism underlying auricular flutter and to rapid impulse formation in one centre or in several centres as that underlying auricular fibrillation, while none are consistent with the assumption of a circus movement

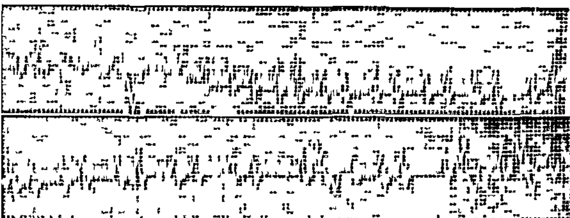


FIG 146 —From an experiment on a dog Auricular flutter with complete A V block during vagal stimulation with alternation in cycle length The two strips are continuous *For further explanation see text* From SCHERF and TERRANOVA *Amer J Physiol*

Our view a departure from the widely accepted theory of circus movement has recently received support from the work of Prinzmetal *et al* (1950) They elicited auricular flutter and fibrillation by the topical application of aconitine that is by the method of Scherf (1947) and arrived at the same conclusions Yet they failed to take any note of the work of Scherf and his collaborators summarized above On the contrary Their solitary reference to the paper by Scherf Romano and Terranova is confined to the technical aspects only Their (Prinzmetal *et al*) failure to mention the results and conclusions of Scherf *et al* creates in those unfamiliar with that work the erroneous impression that they (Prinzmetal *et al*) deserve the credit of priority *

While we consider disputes about priority undesirable we consider it equally undesirable that confirmatory work should by omission of appropriate references pose as original work In this view we are confirmed by an Editorial in the *Ann int Med* to which such readers are referred who wish to obtain an impartial representation of the issue

The claim of Prinzmetal *et al* that auricular fibrillation caused by electrical stimulation can be suppressed by cooling the site of stimulation is at variance with the findings of Scherf *et al* summarized above

Our own position can aptly be described by quoting Lewis Relative to the writer and in justice to the workers in my laboratory I will here state emphatically that *except where by reference it is specifically noted* there is no sentence in our long series of papers nor for that matter in the present chapters which would have been written differently had

* The only other paper quoted by Prinzmetal *et al* regarding the precipitation of arrhythmias by aconitine namely that by Matthews of 1897 is quite irrelevant in connexion with either their or Scherf *et al* s work since Matthews administered this drug intravenously With this method of administration unless the precautions are taken which Scherf detailed in 1979 (*see* p 255) multiform ectopic ventricular beats and ventricular fibrillation appear immediately Furthermore vagal inhibition of the contractions of the auricles which systemic application of aconitine always provokes would make it impossible to study auricular contractions by cinematography which was one of the chief methods employed by Prinzmetal *et al*

his papers as a whole remained unpublished (Lewis s italics 1925 p 295 footnote) The only alterations necessary to make Lewis s statement fully applicable to the matter here under discussion consist in the substitution of the plural for the singular

Ventricular Flutter and Fibrillation

Of the several varieties of flutter and fibrillation ventricular fibrillation was the one to be discovered first (*see* above) Ventricular flutter was discussed only relatively late and its separation from ventricular tachycardia is still far from clear

It was realized at an early stage that fundamental differences exist between auricular and ventricular fibrillation Some of the reasons are not far to seek In the auricles the specialized system is concentrated in two nodes whereas in the ventricles the specialized conducting fibres cover the whole endocardium and permeate the myocardium (*see also* section on Spread p 370) the spread of the excitation through the auricles takes place radially through the common myocardium whereas in the ventricles it is effected by a separate system of paths lastly whereas auricular fibrillation is well compatible with life the ventricular variety results in arrest of the circulation within the heart itself and changes the condition of the heart immediately

Ventricular fibrillation is probably the commonest cause of sudden death and the dramatic role thus played by this arrhythmia was found to stimulate numerous studies about its nature and prevention This important problem is however still far from solved

Note added during proof stage

While this book was in press the monograph of Prinzmetal and his co-workers *The Auricular Arrhythmias* (Thomas Springfield 1952) was published Whereas we do not wish to discuss this book here in any detail we consider it desirable to make some brief references to certain passages dealing with the work of Scherf and his collaborators (pp 104 *et seq* 229)

By quoting out of context single sentences and even part of a sentence Prinzmetal *et al* create the impression that Scherf was unable to draw definite conclusions from his experiments We should have thought that the sentence in Scherf *et al* s paper of 1948 (submitted for publication in May 1947) already quoted in the text of our book

> The result of these experiments could only be explained by assuming that auricular flutter and fibrillation are initiated by rapid impulse formation in a single center (p 250)

is a conclusion the definite nature of which seems hardly questionable Also if Prinzmetal *et al* had read a little further another paper of Scherf *et al* of the same year (1948) which they (Prinzmetal *et al*) quote they would have come across the following sentence in its summary Reference is made to the fact that these observations are incompatible with the circus movement theory of Lewis It can therefore not be doubted that Scherf s conclusions were definite As to the nature of the methods criticized by Prinzmetal *et al* as indirect by which the conclusions were arrived at this is a matter of opinion The whole science of electrocardiography and its clinical application is based on the so-called indirect effect exerted by action potentials on recording instruments and by this an impressive amount of sound physiological and clinical knowledge has been gained In our opinion this method which has made possible a truly astounding progress in cardiology during the last fifty years if used appropriately contrasts favourably—to say the least—with high speed cinematography which in our opinion—we were both able to see such films in our respective countries—proves nothing regarding the finer mechanism underlying auricular arrhythmias The spread of a wave of contraction from the base to the tip of the right auricular appendix whi h the film showed has to be expected whichever theory one accepts A contraction wave spreading up or down the sinus node area was admittedly not visible in the film when aconitine was placed in this region The question arises If a circus movement were present would the contraction of the thin muscle bundles of its—the mother wave s—path become visible in a cinematographic film? We consider that this would be highly improbable and that therefore the absence of such visible contraction along the presumed path of a circulating mother wave does not exclude a circus movement For whatever movements such films may show the nature of the method precludes any observation of the course or spread of excitation unless this gives rise to visible contraction of muscle bundles which happen to be accessible to photography and this can only occur if the size and position of the contracting muscle bundles make this possible

Regarding auricular fibrillation in man we believe that the results of further investigations have to be awaited before the question can be decided whether in the last resort the underlying mechanism is unifocal or multifocal impulse formation

The difficulty in assessing the presence or absence of a circus movement from high speed films was emphasized in a valuable and comprehensive review by Dawes which has just come into our hands (Dawes G S (1952) Experimental cardiac arrhythmias and quinidine like drugs *Pharmacol Rev* 4 43)

The theories of unifocal and multifocal (polytopic) ectopic impulse formation as the mechanism underlying auricular fibrillation were applied also to ventricular fibrillation notwithstanding the recognized differences between auricular and ventricular musculature

On the other hand Garrey and Ashman support the theory that ventricular fibrillation is due to a circus movement Lewis while concluding from the similar appearance of electrograms in auricular and ventricular fibrillation that a similar mechanism is likely to underlie these two arrhythmias pointed out that there was no direct evidence of a wave circulating in

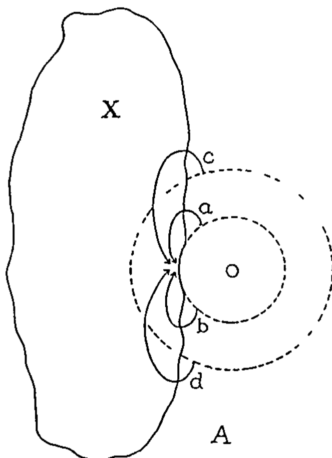


FIG 147 —From ASHMAN and HULL (1945) *Essentials of Electrocardiography* The Macmillan Company New York For explanation see text

the ventricles The suggestion put forward in unequivocal terms by both Mines and Garrey (Lewis) that ventricular fibrillation is due to a circus movement was accepted by Lewis in view of the analogy of the phenomena observed in ventricular and auricular fibrillation But far from considering this as the firmly established mechanism of ventricular fibrillation Lewis wrote Much more work must be undertaken before we can hope to obtain really clear and detailed conceptions of the gravest disorders of the ventricle (1925 p 370) More than twenty five years after these words were written and much work having been done on this problem their message is still true

Mines (1914) put forward this explanation as a result of observing circulating excitation

waves in ventricles of large dogs and of inducing fibrillation in the cooled ventricle of the rabbit s heart by applying a stimulus just at the end of the refractory period Independently Garrey developed a similar theory in the same year Starting from the observations that in small animals (rat rabbit) hearts usually recover from fibrillation whereas in large animals (dogs calf) and in man the reverse is the case and that a certain muscle mass is necessary to sustain fibrillation Garrey assumed that fibrillation is due to circulating excitations in closed intramuscular paths which can only be maintained in masses of adequate size and shape A unilateral spread of excitation is a prerequisite which Garrey assumed to be due to areas of local block

This theory may be illustrated in the form in which it was accepted by Ashman and Hull (Fig 147) In this figure X indicates an area with a refractory period longer than that of the rest of the muscle O is the point of stimulation on the surface of the ventricle With a weak shock applied at O the area indicated by the smaller circle is immediately excited the excitation is assumed to penetrate slowly through the area of increased refractoriness (arrows a and b) and when emerging from it to encounter tissue which is still absolutely refractory so that it cannot re enter the area of the (smaller) circle The result is one extracontraction If on the other hand a relatively strong stimulus is applied at O a larger area indicated by the larger circle is immediately excited Again the excitation wave is assumed to creep round and slowly penetrate into the zone X of increased refractoriness (arrows c and d) but by the time it reaches the boundary of the area which had previously been excited immediately (indicated by the periphery of the larger circle) this need no longer be refractory so that the excitation wave re-enters this circle and thus spreading out from X re activates the whole ventricle As the whole contraction was premature the refractory period of X as elsewhere is shorter than normal which facilitates re entry of the impulse through the paths indicated by arrows c and d

Our objections against the circus movement theory of ventricular fibrillation can be summarized by stating that not only is such assumption purely hypothetical without any experimental proof but also observations made during the last ten to twelve years have emphasized the importance of the vulnerable period and of repetitive response to single or continuous stimuli in accounting for the initiation of ventricular fibrillation The theory of rapid impulse formation in multiple foci moreover far from having been abandoned by its proponents (Ashman and Hull) has received further support by more recent work

The importance of the vulnerable period is discussed in conjunction with allied phenomena more fully in the chapter on Mechanism In the present context it is pertinent to recall the investigations of Wiggers and Wegria who demonstrated that only stimuli falling up to about 0 06 second before the end of contraction (marked by the incisura in the intra ventricular pressure curve) produced ventricular fibrillation Stimuli applied during the isometric relaxation period or subsequent phase of diastole never yielded ventricular fibrillation but only premature beats The vulnerable period extended through a considerable portion of late systole corresponding roughly to the T wave of a standard electrocardiogram By means of studying local electrograms obtained with three pairs of contiguous electrodes it was subsequently found by the same school of workers (Moe Harris and Wiggers) that fibrillation elicited by a very strong brief D C shock was preceded by discrete deflections recurring at progressively decreasing intervals By investigating the order of excitation on the surface and interior of the ventricles during such beats it could be shown that these discrete ectopic beats were due to repetitive emission of several impulses from the stimulated area and were not due to a re entry mechanism Similar conditions were found to prevail regarding the beats initiating ventricular fibrillation produced by anodal polarization (Harris and Moe) In contradistinction to anodal polarization the cathodal one was found ineffective in initiating ventricular fibrillation and this was attributed to the reduction in accommodation by anodal polarization (which is increased by

cathodal polarization) (Regarding accommodation *see* chapter on Mechanism p 504) The reduction in accommodation was also found to be important to account for the observation that local cooling facilitates the development of ventricular fibrillation as a result of single threshold shock stimulation of a non-cooled region during early diastole (Hoff and Stansfield) The ventricular fibrillation itself however as distinct from the initiating series of ectopic beats is assumed by Harris Wiggers and co workers to be due to a re entry of impulses attributable to a progressive decrease in the refractory period combined with a progressive increase in conduction time (Moe Harris and Wiggers) Regarding ventricular fibrillation produced in dogs by coronary occlusion Harris and Rojas demonstrated that a mechanism very similar to that in ventricular fibrillation caused by galvanic current prevails and that the partially ischaemic border seems to be the zone of origin of the ectopic beats Multiple factors are however responsible for ectopic arrhythmias including ventricular fibrillation occurring after coronary occlusion of which sympathetic nerve excitation is one (Harris Estandia and Tillotson)

This problem was investigated in dogs by Scherf *et al* (1950b) by means of the topical application of aconitine crystals to an area of the ventricular surface This resulted within a few minutes in the appearance of ventricular ectopic beats which soon changed into a ventricular tachycardia of three hundred or more resembling ventricular flutter When ever the site of application of aconitine was cooled the tachycardia became slower and then disappeared to re appear when cooling was discontinued This is illustrated in Fig 148

When such ventricular tachycardia had been pre ent for some time it changed into ventricular fibrillation and sometimes but not always this transition was preceded by a sudden increase in rate of the tachycardia Once ventricular fibrillation was established cooling of the site of aconitine application or of any other portion of the ventricular sur face had no effect on the arrhythmia From this the authors inferred that other centres of rapid ectopic impulse formation had become active so that cooling of one centre could no longer abolish fibrillation That during ventricular tachycardia other centres may become active is certain Fig 149 provides an illustration Both Figs 149a and 149b show at their beginning ventricular tachycardia elicited by the application of aconitine to the right ventricle Cooling immediately abolished this tachycardia which is replaced by a slightly slower ectopic tachycardia originating in the contralateral ventricle Similar observations had been made by Scherf (1926) in a different context though interpreted differently at the time

This seems to us to suggest that the primary disturbance in ventricular fibrillation is the rapid impulse formation in several ectopic centres and that the local re entries and inter ferences between such contractions are due to the rapid impulse formation in several centres but not to a circus movement While Wiggers and his co workers put the emphasis on the progressive increase in conduction time associated with a reduction in the refractory period resulting in local block areas and circus movements we would stress the simultaneous activity at a high rate of several ectopic centres as the essential prerequisite

Without wishing to enter into a detailed discussion of all points which have been adduced in support of the circus movement theory of ventricular fibrillation two may be singled out as having been considered by some to be particularly important

1 The observation that a certain muscle mass is necessary for fibrillation to occur was regarded as alone almost sufficient to disprove the theory that fibrillation is due to focal impulse formation This argument is unacceptable to us since it was found in certain experi mental conditions that auricular or ventricular fibrillation occurred in the dog s heart when ever the ectopic auricular or ventricular rate respectively exceeded 600 per minute (Scherf Scharf and Goklen Scherf *et al* 1950b) It is only with rates above a certain figure that precisely as a result of this high rate of impulse formation the islands of refractory tissue occur which Lewis Feil and Stroud have demonstrated in such conditions (*see also* Lewis s



FIG 148 —From an experiment on a dog Ventricular tachycardia precipitated by the topical application of aconitine crystals to an area of the ventricular surface *Suppression of the tachycardia by cooling the site of application with subsequent re appearance of the tachycardia after cooling was discontinued*

a

b

FIG 149 —From an experiment on a dog The beginning of both strips show ventricular tachycardia elicited by the application of aconitine to the right ventricle Its suppression by cooling the site of application resulted in a ventricular tachycardia originating in the contralateral ventricle

diagrammatic illustration 1921 1925 Fig 306) In our opinion it is the high rate of impulse formation which is the primary factor A certain muscle mass is necessary for a sufficient number of islands of refractory tissue of the requisite size to occur We do not dispute the possibility or even probability of local re entries in established fibrillation but we do not believe that local circus movements either initiate fibrillation or are the primary factor in perpetuating it

2 The termination of ventricular fibrillation by a strong electrical shock has been held to prove a circus movement underlying this arrhythmia it being assumed that the termin ation is due to abolition of the gap of excitable tissue between the head and tail of the circulating wave We have already drawn attention to one objection to this interpretation in connexion with auricular fibrillation namely that only a shock *properly timed* has this effect If the above reasoning were correct such shock should always terminate fibrillation irrespective of its timing which is not the case It may here be added that if a focal origin of impulse formation is assumed to underlie ventricular fibrillation the abolition by a properly timed shock can be understood in a variety of ways For instance depolarization of the foci with consequent change in the sequence and rate of impulse formation so that excitations no longer occur at the same rate or fall within the supernormal phase of preceding beats would be one possibility

In conclusion we may state our belief that none of the observations made in connexion with the initiation and establishment of ventricular fibrillation can be regarded as proving an underlying circus movement many objections against this theory are discussed in this section On the other hand we are not aware of any observations which could not be under stood as the result of rapid impulse formation in circumscribed foci resulting in local areas of depressed conductivity and local re entries these being due to the high rate Such con ception is in accordance with a wealth of observations made on nerve and cardiac muscle of the latter the work of Lewis and collaborators published over thirty years ago is not the least important

Repetitive response to single and continuous stimuli is more fully discussed in the chap ter on Mechanism

SUMMARY

The three main theories of the mechanism underlying auricular and ventricular flutter and fibrillation are briefly reviewed namely the theory of dissociated action of various groups of muscle fibres that of tachysystoly and of circus movement The reasons are dis cussed why until recently the circus movement theory was widely accepted to explain *auricular* flutter and fibrillation in spite of weighty objections raised against it almost from *the start these are discussed in some detail More recent work employing the experimental* production of such arrhythmias by means of the topical application of aconitine have yielded results which are incompatible with the circus movement theory and strongly suggest that auricular flutter is due to the rapid impulse formation in one circum scribed ectopic centre This work is discussed in detail Auricular fibrillation cannot be considered as being due to one uniform mechanism Reasons are given for the assumption that this arrhythmia if precipitated by the topical application of aconitine is due to rapid stimulus formation in one ectopic centre whereas if it is elicited by electrical stimulation of or topical application of acetylcholine or veratrine to the auricles ectopic impulse for mation occurs in several ectopic centres Regarding *ventricular* fibrillation the importance of the vulnerable period in late systole and early diastole is emphasized during which alone single stimuli produce ventricular fibrillation It is pointed out that this is one instance of repetitive response to a single stimulus some relevant work on this is discussed whilst the reader is referred to the chapter on Mechanism for a fuller discussion of this

phenomenon The observation is described and illustrated that during ventricular tachy cardia the activity of one ectopic centre may awaken that of others Evidence is discussed in support of the view that in ventricular fibrillation the primary factor is the simultaneous activity at a high rate of several ectopic centres of impulse formation resulting in local areas of depressed conductivity and local re entries but is not a circus movement

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PAROXYSMAL TACHYCARDIA

Paroxysmal tachycardia is universally regarded as an arrhythmia due to a number of extrasystoles occurring in succession The close relation between this disturbance of rhythm and extrasystoles has been recognized for a long time and is discussed in several papers published at the beginning of this century (Mackenzie 1902 Hoffmann 1903 Pan 1904 Lewis 1914) It is a common experience that attacks of paroxysmal tachycardia are preceded and followed by single extrasystoles which in the electrocardiogram have the same shape as the beats composing the paroxysm Furthermore the first beat of the paroxysmal tachycardia usually has the same fixed coupling as the single extrasystoles

Paroxysmal tachycardia thus being composed of individual extrasystoles occurring in succession it is easily understood that as far as the site of origin is concerned all types of this arrhythmia have been observed as they are known regarding single extrasystoles The commonest is the supraventricular one usually auricular in origin but A V nodal attacks as well as ventricular ones are well known the last usually having a far more serious prognostic significance than the others

Many varieties of paroxysmal tachycardia have been reported Thus this arrhythmia may occur in association with complete A V block (Singer and Winterberg Barker *et al* Case 16) or with ventricular extrasystoles (Samet and Schott) ventricular paroxysmal tachycardias with retrograde conduction to the auricles have been reported often with some degree of retrograde block (Allan Mahaim and Barrelet) The duration of the attacks may vary from a few seconds to many hours or even days and equally great variations occur in their rate of incidence It is therefore no exaggeration to say that there are no two patients in whom such attacks are identical but in the same patient the same kind of attack may be observed over many years

Since the essential reason for including paroxysmal tachycardia in this book is the close association of this arrhythmia with extrasystoles a detailed discussion of the countless varieties of its features would be outside the scope of this book A few special types may however be briefly discussed

It was Gallavardin to whom credit is due for having described many important forms of this arrhythmia According to him (Gallavardin 1922a) the classical variety (type Bou

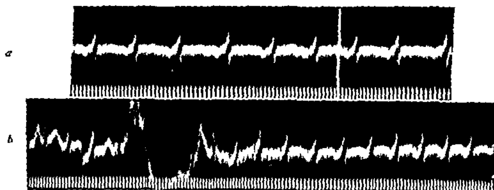


Fig 150 – Paroxysmal tachycardia arising in the coronary sinus area *a* before exercise rate 136 *b* after twenty genuflexions increase in rate to 214

veret) has no relation to single extrasystoles since no isolated ectopic beats are observed between attacks in such patients While this is true for quite a proportion of instances we do not think that from a point of view of underlying mechanism or clinical significance any distinction is justified between those cases and others in whom occasional isolated extra systoles are recorded

Gallavardin described two further types of paroxysmal tachycardia which in our opinion constitute definite clinical entities

1 The *tachycardie a centre excitable* (Gallavardin 1922a) In this variety the individual attack is short and can easily be elicited by exertion or emotion Exertion may lengthen the duration of such attacks as well as increase their rate Ventricular (Scherf and Weissberg Wenckebach and Winterberg Wilson *et al*) and auricular (Scherf and Weissberg) varieties of this arrhythmia have been described

Fig 150 shows such an instance in which the arrhythmia originated in the coronary sinus Exertion (20 genuflexions) increased the rate from 136 to 214 per minute

2 *Extrasystolie a paroxysmes tachycardiques* was described in its auricular and ventricular varieties by Gallavardin in the same year (1922b 1922c) This type is characterized by the features that the individual paroxysm is short consisting of series of 20–200

extrasystoles in succession such paroxysms being separated by only a very few sinus beats often only one rarely more than three Clinically the individual attack is therefore short lasting not more than a minute or two but as soon as one attack stops the next one starts after a very brief respite One peculiarity of this condition is that it tends to continue in the same fashion for many years Gallavardin observed a patient with the ventricular variety for seven years we followed one with the same condition for five years Another patient with auricular paroxysmal tachycardia of this kind was under our observation for six years and Parkinson and Papp—who called it repetitive paroxysmal tachycardia—reported such paroxysms during ten years of an eighteen years period of observation

Fig 151 provides an example of the ventricular form of this arrhythmia and clearly demonstrates the shortness of the attacks separated by only one sinus beat

Fig 152a illustrates the auricular variety emphasizing also the diagnostic difficulties Actually in the report of the cardiographic department of the hospital where a first short record was obtained from this patient a diagnosis of S A block was made Longer records reproduced in Fig 152a show however that what might appear at first sight to be S A block is in fact normal sinus rhythm The P waves of the tachycardia resemble the sinus

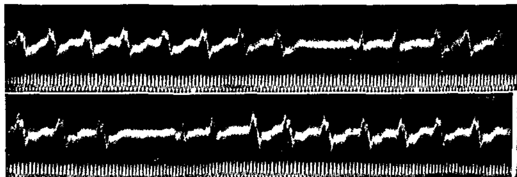


Fig 151 —Extrasystolie à paroxysmes tachycardiques ventricular form The two strips are continuous

P waves so closely in most leads that sinus tachycardia seems to prevail While close inspection of the P waves during tachycardia reveals in some leads only some minute differences in shape compared with the P waves during slow cardiac action these are fairly obvious in lead CR 1 in which the P waves of sinus beats are high and peaked whereas those during tachycardia are much lower and round Comparison of Fig 152a with 152b recorded from the same patient one week later during sinus rhythm confirms the diagnosis that the condition reproduced in Fig 152a was in fact auricular extrasystolie a paroxysmes tachycardiques

This arrhythmia is usually found in otherwise healthy individuals Parkinson and Papp who reported forty cases of this kind including four of flutter and one of fibrillation gave it as their opinion that the condition may be regarded as a distinctive disorder of rhythm rather than a cardiac disease of consequence While it is true that in some patients such attacks disappear after a varying period of time in others the tachycardia gradually produces cardiac dilatation with relative mitral and tricuspid regurgitation and may terminate in death due to congestive heart failure (Scherf and Kisch) We would therefore advocate a somewhat more guarded prognosis This is also justified in view of the notorious difficulties in the treatment of this arrhythmia which responds poorly or not at all to quinidine or digitalis And even in those cases which do react favourably to one or the other of these

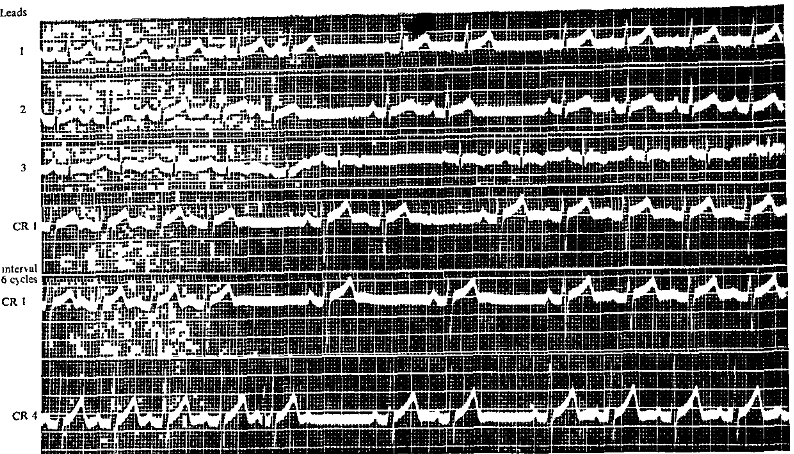


Fig 152*a*
Extrasystolie à paroxysmes tachycardiques auricular form

drugs neither can be given indefinitely and as soon as the effective remedy is stopped the arrhythmia recurs

Tracings of this type of tachycardia are also reproduced in Figs 175 and 200

Practically the same variety of paroxysmal tachycardia has also been termed tachy cardie en salves (Gallavardin and Dumas 1924 Gallavardin and Veil 1927 1929 a and b Lutembacher 1929)

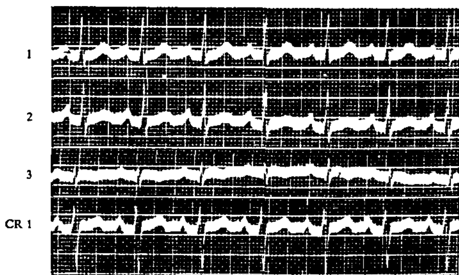


Fig 152*b*

From the same patient as Fig 152*a* recorded one week later sinus rhythm For further explanation see text

Paroxysmal Supra Ventricular Tachycardia with A V Block

Until recently it was thought that with rare exceptions in supraventricular paroxysmal tachycardia the ventricles respond to every supraventricular stimulus This was in fact considered to be one of the essential differences between paroxysmal tachycardia and auri cular flutter as in the latter some degree of A V block constant or varying is nearly always present While sporadic cases of paroxysmal tachycardia with A V block had been reported since Koplik s first communication in 1917 it was realized only in 1943 that this condition is by no means rare when Barker Wilson Johnston and Wishart collected seventeen such cases from the literature and added eighteen observations of their own In a subsequent paper they reported alternation of cycle length in this type of arrhythmia which they inter preted as suggesting a circus movement with involvement of either the S A or the A V node (Barker Johnston and Wilson Barker Wilson and Johnston) This group of workers amplified this conception by stating that such circus movement is of a special kind for the following reasons slowing of the auricular rate and termination of the attacks by vagal stimulation and by digitalis acceleration of the rate by exercise the relatively slow rate and long cycle length and the separation of the auricular deflections by isoelectric intervals (Regarding our views on this *see* below) In the same year Decherd Herrmann and Schwab reported a series of forty cases with this arrhythmia and subsequently Decherd and Herrmann (1944) pointed out that paroxysmal tachycardia with block was associated with auricular flutter or fibrillation far more frequently than the variety without block such association was found in twelve out of forty two cases of paroxysmal tachycardia with A V

block (28 6 per cent) compared with only two in seventy cases without block In view of the theory then generally accepted that auricular flutter and fibrillation were due to a circus movement such observations tend d to suggest that paroxysmal tachycardia at least the variety with A V block was due to the same disturbance Evans who reported a series of twenty seven cases of paroxysmal tachycardia with A V block emphasized the unity be tween paroxysmal tachycardia and auricular flutter However by determining the momen tary atrial electrical axis for each 0 01 second Decherd Ruskin and Herrmann failed to find any evidence of circus movement in this arrhythmia and concluded that the weight of evidence points to the existence of an ectopic site of impulse generation These authors also found considerable differences in the momentary atrial electrical axis between paroxys mal tachycardia with A V block and auricular flutter (See also Fig 163*a*)

Fig 153 illustrates a comparatively rare variety of this arrhythmia namely paroxysmal supra ventricular tachycardia with periodically dropped ventricular beats (Wenckebach s periods) It was recorded in a man with rheumatic mitral and aortic valvular disease

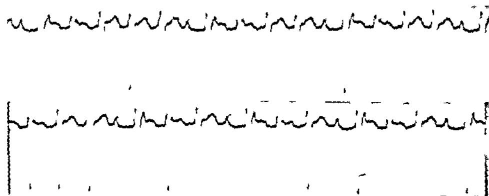


Fig 153 —Lead V 1 The two strips are continuous Paroxysmal supra ventricular tachycardia with periodically dropped ventricular beats (Wenckebach s periods)

It should be recalled that the above conclusions in respect of paroxysmal tachycardia with A V block were drawn at a time when the theory of circus movement of auricular flutter was almost universally accepted If in spite of the closer association between paroxysmal tachycardia with block and auricular flutter no evidence of circus movement was found in the former such mechanism would *a fortiori* seem far more unlikely to account for the ordinary variety of paroxysmal tachycardia without block However this problem is still controversial and its general aspects warrant a more detailed discussion

Mechanism of Paroxysmal Tachycardia

At the beginning of this section the close association between extrasystoles and paroxys mal tachycardia is emphasized the borderline between multiple extrasystoles and a short attack of paroxysmal tachycardia is but vaguely defined Any attempt to explain the mechanism of paroxysmal tachycardia must have as its starting point the conception that this disorder of rhythm consists of a series of extrasystoles occurring in succession Thus we seem justified in regarding paroxysmal tachycardia and extrasystoles at all events in their usual forms as alike genetically Lewis 1925 p 386 Lewis also pointed out that this idea was originally mooted by Hoffmann (1903)

In regard to the mechanism underlying these arrhythmias Lewis the protagonist of the theory of circus movement in auricular flutter and fibrillation later saw difficulties in applying this explanation to paroxysmal tachycardia the crucial obstacle being that the auricle has no sufficient tract of tissue to maintain a simple circus movement for a half second if a reasonable conducting rate is allowed (1925 p 397)

In contradistinction to the very cautious way in which Lewis discussed the mechanism of this arrhythmia Ashman and Hull while not denying that occasionally it may be due to a rapidly acting ectopic pacemaker considered a circus mechanism often though not always responsible They thought it probable that in the auricular variety the circuit is into and out of the S A node whereas in the junctional type it was probably often due to an impulse re entering the A V node In support of this view they pointed out that the termination of such attacks by vagal stimulation could easily be understood by the strong vagal effect on these nodes whereas such vagal action was inexplicable if ectopic focal impulse formation were assumed While for reasons discussed below in this section we do not think that a circus movement underlies paroxysmal tachycardia we admit that the effect of vagal stimu lation in terminating such paroxysms is difficult to understand a tentative explanation is mentioned below As already stated Barker *et al* also favour the conception of a circus movement being responsible for paroxysmal tachycardia in view of their observation of alternation of cycle lengths during the paroxysms since there were no published examples of alternation in cycle length which have been clearly shown to depend solely upon the dis charge of impulses by a single centre However since this statement was made it has been demonstrated that ectopic stimulus formation in a centre may be associated with alternation in cycle length (Scherf and Terranova *see* Fig 146 Scherf Chick *et al*)

While we believe that in some rare cases a circulating excitation may produce tachycardia in the manner discussed in connexion with return extrasystoles (*q v*) the vast majority of instances of paroxysmal tachycardia are in our opinion due to ectopic impulse formation *This view is based on the following considerations*

1 To a certain extent the circus movement theory as an explanation of paroxysmal tachycardia has been considered in view of the analogies between this disorder of rhythm and extrasystoles flutter and fibrillation Since for reasons fully discussed in the appro priate sections and chapters we do not believe that with rare specified exceptions any of these arrhythmias are due to a circus movement but are a result of ectopic impulse for mation in a circumscribed centre this argument becomes invalid

2 Warming of the focus of origin of extrasystoles elicited by the topical application of various compounds (sodium or barium chloride digitalis or strophanthin) results in paroxysmal tachycardia which lasts for the duration of the warming of the focus This and similar observations discussed in the chapter on Mechanism strongly support the focal origin of such arrhythmias and cannot be reconciled with the theory of circus movement

3 The order of the cycle lengths between individual beats during paroxysmal tachy cardia particularly in the auricular variety precludes a circus movement This point based on Lewis s views discussed above seems to us a very strong argument against the circus movement theory

4 The observation of a sudden doubling of rate during paroxysmal tachycardia from 107 to 214 (Camp and Scherf) (*see* Fig 154) contains two arguments against the circus movement theory a rate of 107 cannot be due to a circus movement in view of the long cycle length (0 56 second) moreover a sudden change of path of the presumed circus movement to one of half the former length is an assumption which is unacceptable for the same reasons which were discussed in presumed similar conditions of auricular flutter (p 223) This observation is far better explained by assuming ectopic focal impulse

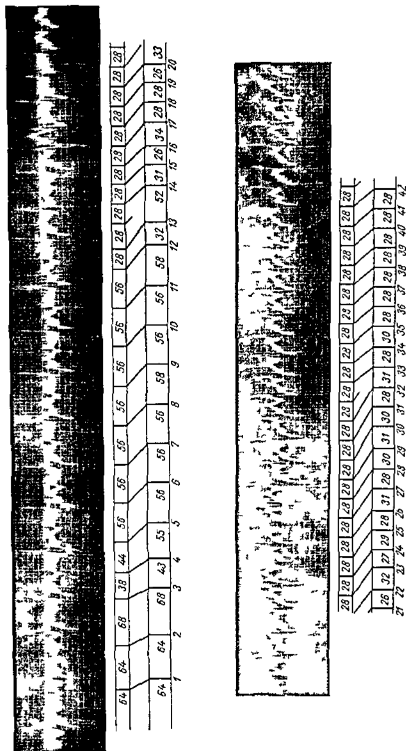


Fig 154.—Sudden doubling of rate during paroxysmal tachycardia From Camp and Scherf *Wien Arch inn Med*

formation whereby during the slower rate either a 2 1 block was present or every second impulse failed to be initiated (*see* chapter on Mechanism)

5 The sudden dropping of a beat during tachycardia is incompatible with the circus movement theory Such observations were made in cases of auricular (Gallavardin 1946 Figs 70 and 71 on pp 130/1) and ventricular (Fig 108) tachycardia This phenomenon can be understood by assuming rapid focal ectopic impulse formation with occasional block or occasional failure of one impulse to be initiated

6 The observation that paroxysmal tachycardia may be associated with dissociation with interference (Schott) (Fig 155) can hardly be understood in conjunction with a circus movement but presents no difficulty if focal impulse formation is postulated

We therefore believe that the series of ectopic beats which constitute paroxysmal tachycardia originate in the same way as we assume all extrasystoles (in the strict sense of the term) to arise namely by being precipitated in an ectopic focus by the last preceding beat With the exception of the first beat of such paroxysms which is an extrasystole with fixed coupling initiated by a sinus beat the only difference is that in paroxysmal tachycardia the precipitating beat also is of ectopic origin In our opinion all these beats arise in the

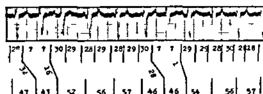


FIG 155 —Lead CR 1 Paroxysmal auricular tachycardia with dissociation with interference From SCHOTT *Proc roy Soc Med*

same circumscribed ectopic focus A circus movement not only is not proved but—apart from rare exceptions—is unlikely in view of *all* the evidence which we are discussing against this theory in connexion with extrasystoles

If the same mechanism that is rapid stimulus formation in one ectopic centre underlies auricular flutter (and some forms of auricular fibrillation) as well as paroxysmal tachycardia the different effect of vagal stimulation requires an explanation Regarding clinical paroxysmal tachycardia it is well known that carotid sinus pressure either abolishes the arrhythmia and restores sinus rhythm or has no effect In clinical flutter on the other hand carotid sinus pressure never has this effect and in experimental flutter vagal stimulation usually increases the rate of ectopic impulse formation and in certain conditions converts flutter into fibrillation This is however by no means invariable In flutter elicited by faradic stimulation of the auricles (Lewis *et al*) or by aconitine (Scherf Blumenfeld and Mueller) faradic stimulation of the vagus abolished flutter in rare instances While we believe that the different clinical response of these two arrhythmias to carotid sinus pressure alone justifies a separation between these two groups of auricular arrhythmias—the unity of which tends to be emphasized of late—a satisfactory explanation of the mechanism accounting for the difference in vagal action cannot be offered The tentative hypothesis has been advanced that in auricular flutter the stimulus is a constant one the response to which depends essentially on the refractory phase of the auricle whereas in auricular paroxysmal tachycardia the stimulus is more rhythmical and thus more akin to the normal stimulus in the S A node in both conditions vagal stimulation having an inhibitory effect (Scherf and Terranova) But this is admittedly not more than conjectural

Differential Diagnosis

While the general diagnostic principles of paroxysmal tachycardia will not be discussed a few remarks about differential diagnosis should not be amiss

The differential diagnosis of an individual attack of tachycardia of this kind must be made

(a) between paroxysmal tachycardia and other disorders of rhythm associated with a high ventricular rate and

(b) between the various types of paroxysmal tachycardia according to the site of origin of the ectopic beats

Regarding (a) In practice the most frequent difficulty arises in the differentiation between paroxysmal tachycardia and auricular flutter which at the same time presents also the greatest theoretical difficulties In both the ventricular rhythm may be regular or irregular and in both often is regular Until it was realized that A V block is not infrequently associated with paroxysmal tachycardia these two arrhythmias were separated by the presence or absence of A V block this distinction is now no longer valid While we believe that these two arrhythmias are separate entities because an attack of paroxysmal tachycardia can often be stopped by way of reflex whereas all such procedures are without effect in flutter we prefer to admit that none of the criteria adduced for making the distinction electrocardiographically can be considered reliable (*see* for instance Israel and Mazzei) To cite just one example According to Evans in auricular flutter the auricular rate is slower than in paroxysmal tachycardia whereas according to Decherd *et al* (1943) the reverse is the case We consider it necessary to await the result of further studies before considering it possible to state distinguishing criteria with any degree of certainty Fortunately this gap in our theoretical knowledge does not interfere with treatment

Regarding (b) The site of origin of paroxysmal tachycardia can often be determined by the usual electrocardiograms particularly by chest leads taken from points 1 (and 2) or special chest leads (manubrium–xiphoid) In auricular paroxysmal tachycardia the ventricular complexes often are of normal shape but aberrant intraventricular conduction of supraventricular impulses may closely simulate ventricular origin of the tachycardia Furthermore in a considerable proportion of cases the P waves are buried in the QRS complex or T wave of the preceding beat and thus not discernible this may lead to the erroneous diagnosis of atrio ventricular tachycardia Unless auricular origin can definitely be excluded by special leads of which oesophageal leads must be mentioned as being particularly valuable in all kinds of auricular disorders of rhythm it is preferable to use the term supraventricular tachycardia The same considerations obtain as in auricular extrasystoles (*see also* section on Incidence)

Regarding the differentiation between supraventricular tachycardia with aberrant intraventricular conduction and ventricular tachycardia the finding of a slower independent auricular rhythm associated with a fast ventricular one with abnormally shaped complexes establishes the diagnosis of ventricular origin This is however not possible in every case Another distinguishing factor can be established if isolated extrasystoles are observed between attacks these are usually from the same focus which gives rise to the tachycardia

That retrograde conduction may occur in ventricular tachycardia has already been referred to earlier in this section

From the point of view of prognosis and treatment the essential pre requisite is to determine whether an attack is supra ventricular or ventricular in origin

Treatment

Supra Ventricular Paroxysmal Tachycardia

In the common variety of such attacks that is without A V block the first approach should always be to stop the tachycardia by one of the manoeuvres which often terminate such paroxysms by way of reflex the efferent path being the vagus It is true that as discussed in the chapter on extrasystoles and the nervous system stimulation of vagus or sympathetic may abolish or precipitate ectopic arrhythmias also in man but in clinical practice stimulation of the vagus by way of reflex as a rule terminates ectopic supra ventricular tachycardias whereas that of the sympathetic for example by adrenaline usually has the reverse effect

The most important methods for eliciting such Reflexes in clinical practice are

1 CAROTID SINUS REFLEX Pressure is applied *exactly* at the site of the bifurcation of the carotid artery The correct level is found by determining the point of intersection of the carotid artery with the horizontal at the level of the upper border of the thyroid cartilage but as the exact site of the carotid sinus varies somewhat in different individuals attempts at compressing at a slightly higher or lower level have to be made if the first trials are unsuccessful It is best to put the four fingers of one s hand behind the patient s neck and exert pressure with the thumb by gently but firmly compressing the artery downward and medially towards the spine In the majority of cases pressure on the right is more successful than on the left but in a minority the reverse is observed Pressure should always be carried out with the patient in the supine position and never on both sides simultaneously While pressure is exerted the heart action should be kept under observation by auscultation and pressure immediately released when the tachycardia stops if this occurs it does so suddenly

The degree of pressure which has to be employed varies greatly in different patients In elderly subjects with arteriosclerotic arteries merely touching the skin over the carotid sinus may terminate an attack in others stronger pressure maintained up to half a minute may be necessary Untoward effects arising from carotid sinus pressure have been reported for instance fainting hemiplegia or dangerous cerebral anoxia but these can be minimized by strictly adhering to the rules mentioned above Special caution is necessary in patients with pronounced arteriosclerosis

The proportion of attacks which can be terminated in this way is considerable If this method is at first unsuccessful it may prove effective if repeated after a time particularly if in the meantime the patient was given quinidine or digitalis (*see* below) But drug treatment should be resorted to only after carotid sinus pressure and similar procedures discussed immediately below had been given a fair trial in our opinion drugs are often given unnecessarily

Most observers agree that carotid sinus pressure is ineffective in cases of ventricular paroxysmal tachycardia and this is easily understood in view of the absence of a direct vagal effect in the mammalian ventricle Exceptions to this rule have however been reported Thus in an observation published by Wenckebach and Winterberg (1927 Plate 190) carotid sinus pressure precipitated as well as suppressed ventricular tachycardia Other unusual observations include the transient development of ventricular tachycardia before restoration of sinus rhythm by carotid sinus pressure in two cases of supraventricular tachycardia (Meredith and Beckwith) and carotid sinus pressure terminating as well as precipitating supra ventricular tachycardia in the same patient (Blumenfeld *et al*)

2 OCULO CARDIAC REFLEX This manoeuvre may abolish an attack in patients in whom other procedures had failed to do so The patient is asked to look downward and close his eyes pressure is then exerted simultaneously on both eyeballs

3 PULMONO CARDIAC REFLEXES The simplest of these is precipitated by taking a deep breath Not infrequently this suffices to stop an attack In one of our patients a seventy two year old lady who for many years had an average of sixteen attacks a day every paroxysm could be terminated in this way In his textbook on cardiac diseases Bamberger mentioned this measure as early as 1857 In some comparatively rare cases deep breathing precipitates such attacks In other patients Valsalva s experiment is successful while deep breathing has no effect this manoeuvre too may in rare instances fire off such attacks (Galli)

4 OTHER REFLEXES One of the most useful measures is the gagging reflex elicited by the patient s putting his fingers in his throat It is as effective as vomiting which some authors advocate to induce artificially by drugs (for example apomorphine) but without the undesirable side effects

In some patients attacks of supraventricular tachycardia can be stopped by deep bending crouching pressure on the abdomen or drinking iced water

Different individuals vary greatly in their response to any of these measures and each patient soon finds out for himself which is the most effective They all have this important point in common that the patients can learn to carry out themselves whatever manoeuvre they have found best The psychological effect of this in addition to avoiding by the timely termination any somatic effect caused by prolonged attacks is by no means negligible

Drugs Drugs should only be employed if all the above measures have been tried not only at the beginning of an attack but at intervals during such paroxysms and failed Moreover such procedures may become successful when resumed in conjunction with drugs

There is hardly a drug which has not been mentioned as successful in suppressing such attacks but in practice only three can be recommended quinidine digitalis and magnesium sulphate in this order

Quinidine As initial dose we recommend quinidine sulphate 0 2-0 4 gramme by mouth to be repeated at intervals of three hours as long as necessary and provided no signs of cinchonism occur (*see* section on Treatment p 475) In the majority of patients this regime will terminate the attack within a short time If necessary the above dose can be repeated one hour after the initial dose or given at two hourly intervals

In patients with frequent attacks preventive treatment by giving 0 2 gramme every four hours is often successful If necessary medication is continued during the night It is not at all rare to find that after a time medication can gradually be reduced and subsequently discontinued without attacks recurring

The intravenous injection of quinine or quinidine is not free from risk and hardly ever necessary Only in patients with greatly prolonged attacks in which the arrhythmia aggravated pre existing heart failure to the point of danger should this method be considered which can yield spectacular results (Samet and Schott) The single dose varies between 0 2 and 0 5 gramme

Digitalis takes only second place since its action is not so specific as that of quinidine It is true however that oral digitalization or the intravenous injection of a purified glucoside often abolishes an attack promptly This drug can also be used if supraventricular paroxysmal tachycardia develops after coronary occlusion and contrary to the popular belief it is also effective if a ventricular tachycardia occurs in such circumstances (*see* below)

The dosage varies widely in different cases We recommend 1 mg digoxin by mouth as initial dose followed by 0 25 mgm at six hourly intervals the patient being kept under careful observation for change in rhythm and signs of digitalis overdosage (p 477) Instead of digoxin digitoxin may be used 0 1 mg of digitoxin being equivalent to 0 25 mgm of

digoxin If intravenous injections are resorted to we recommend 0 5 mgm digoxin in 10 0 cc followed by 0 25 mgm at six hourly intervals given by mouth Oral digitalization can be started at the time of the injection Instead of the intravenous injection of digoxin that of 0 25 mgm strophanthin may be given followed by the same dose after twelve hours if no untoward effects occur oral digitalization should be started at the same time (0 5 mgm digoxin as initial dose followed by 0 25 mgm at six hourly intervals) Strophanthin should never be given if the patient had received digitalis within the preceding ten days and we do not recommend to exceed the doses stated

Magnesium sulphate This has proved useful in doses of 15 0—20 0 cc of a 20-per cent solution given intravenously in supraventricular and ventricular tachycardias (Boyd and Scherf)

Other drugs will be discussed only shortly since their effect is either not convincing or they cause unpleasant side effects

Choline and derivatives may be mentioned in the first place Of these acetylcholine (Schliephake Boden and Wankell Abbott Segers *et al*) and particularly acetyl beta methylcholine (Starr Morgan) were used but in view of the unpleasant side effects this treatment is now used only rarely Acetyl beta methylcholine is given hypodermically in doses of 10–30 mgm (20–50 mgm Morgan) A syringe for the intravenous injection of atropine (grain 1/50) should always be ready as antidote For further details the reader is referred to the papers by Starr and by Morgan

Similarly prostigmine methylsulphate (0 5–1 0 mgm) (Battro *et al*) or neostigmine (1 mgm Waldman and Pelner) both given intravenously have been recommended These drugs too produce undesirable side effects

Other drugs which have been recommended but the use of which we should like to discourage are epinephrine atabrine fagarine and calcium salts The intramuscular injection of paredrine hydrobromide (20 mgm Griffith) or the intravenous injection of neo synephrine (0 5 mgm) seem less risky but in view of the possible considerable rise in blood pressure precipitated by the latter (Youmans *et al*) we do not recommend their use

The efficacy of procaine amide (Pronestyl) in the treatment of auricular paroxysmal tachycardia is not yet established and, while it seems promising to a certain extent we should like to await further reports before expressing an opinion

Further particulars about most of the drugs mentioned will be found in the appropriate sections of the chapter on Drugs

In conclusion we would advocate a healthy scepticism against any new drugs recommended for the treatment of paroxysmal tachycardia

All these remarks about treatment apply only to supraventricular paroxysmal tachycardia without A V block The variety with block is far more difficult to treat The response of such patients to carotid sinus pressure quinidine or digitalis is often poor and transient The most effective therapeutic measures have to be established in each case by trial and error

Similar difficulties are experienced in the treatment of extrasystolie à paroxysmes tachycardiques as already referred to

Ventricular Paroxysmal Tachycardia

It is universally recognized that this variety of paroxysmal tachycardia carries a far more serious prognosis than the supraventricular type since it is mostly associated with structural heart disease and is a dreaded complication of myocardial infarction While every effort must be made to stop it as quickly as possible mention should be made of the increasing number of instances in which this arrhythmia has been reported in individuals with otherwise healthy hearts Thus thirteen out of 107 cases reported by Armbrust *et al* had no heart disease and in a further five the co-existence of the Wolff Parkinson White syndrome made

the evaluation of the type of arrhythmia and its significance doubtful Reports of single cases of this kind are those of Stein and Driscoll and of Mahaim and Perusset The role played by digitalis overdosage in the production of this arrhythmia must not be forgotten

Regarding treatment all the measures based on reflexes which were discussed in connexion with supraventricular tachycardia are ineffective with rare exceptions The drug of choice is quinidine In many cases oral medication is effective We recommend 0 2 gramme as initial dose and if no untoward effects occur 0 4 gramme can be given every 2–3 hours If the arrhythmia persists after six hours the single dose can be increased to 0 6 gramme In exceptional cases much larger doses have been given for example the maximum single dose employed by Armbrust *et al* being 2 5 grammes! If however the ventricular tachycardia occurred in association with myocardial infarction and is not terminated within six hours the intravenous injection of quinidine in doses varying between 0 2 and 0 3 gramme is indicated and justified the risk inherent in the arrhythmia in such circumstances outweighs the risk of the intravenous injection This method may however be superseded by procaine amide (Pronestyl) which has recently been introduced and has proved most successful in the treatment of this dangerous condition in some cases it was superior to quinidine The doses recommended on the grounds of observations so far available are If given by mouth 1 25 grammes as initial dose followed in one hour by an additional 0 75 gramme if the tachycardia persists In the majority of cases this proved adequate to terminate the tachycardia but if necessary subsequent doses of 0 5–1 0 gramme at two hourly intervals may eliminate the arrhythmia When given intravenously the drug should be injected very slowly the maximum rate being 100 mgm per minute or less the dose varied in different cases between 200 and 1 000 mgm (that is between 2 and 10 cc of the Pronestyl solution as supplied by the manufacturers) Continual observation of blood pressure and electrocardiogram during the injection is necessary with the intravenous route and the injection should be discontinued immediately if a more pronounced fall in blood pressure occurs or the arrhythmia stops (*See also* section on Cocaine)

Gonzalez Sabathie reported good effects in nine out of ten cases from the intravenous injection of 0 01 to 0 04 gramme of morphine

By most authors digitalis is considered contra indicated in ventricular tachycardias but in this general form this view is certainly not correct Scherf and Kisch found in one of their cases with ventricular tachycardia and alternating shape of the complexes in the electrocardiogram that the arrhythmia could invariably be abolished by digitalis Gibson and Schemm reported good effects from large doses of digitalis (mostly digitoxin) in four observations made on three patients with ventricular tachycardia after myocardial infarction and our observations are in accordance with that of those authors We may summarize our views on this subject by stating that in ventricular tachycardia provided the arrhythmia is not due to digitalis this drug if otherwise indicated can be given far more freely than hitherto assumed and that in such cases it often abolishes the disturbance of rhythm

SUMMARY

The close relation between paroxysmal tachycardia and extrasystoles is emphasized and while a detailed description of the countless varieties of this arrhythmia is considered outside the scope of this book some special types are briefly discussed namely tachycardie a centre excitable extrasystolie a paroxysmes tachycardiques and paroxysmal supraventricular tachycardia with A V block The mechanism of paroxysmal tachycardia is discussed in some detail and reasons are given for our contention that this arrhythmia is due to impulses arising in a circumscribed ectopic focus and not due to a circus movement The mode of origin of paroxysmal tachycardia is thus assumed to be essentially the same as that of extrasystoles Some points presenting special difficulties in the differential diagnosis between

paroxysmal tachycardia and auricular flutter and between supraventricular atrio ventricular and ventricular paroxysmal tachycardia are briefly discussed

The treatment is discussed in some detail under the following headings

Supraventricular paroxysmal tachycardia It is pointed out that such paroxysms can be terminated by way of reflex in a considerable proportion of cases such reflexes are reviewed Drug treatment should only be resorted to after such procedures had been given a fair trial Amongst the great number of drugs which have been reported as sometimes successful in practice only three can be recommended quinidine digitalis and magnesium sulphate in this order Details of dosage and administration are given Other drugs are briefly mentioned though not recommended

Ventricular paroxysmal tachycardia The treatment of choice is quinidine but procaine amide (Pronestyl) recently introduced may to a certain extent replace quinidine in the treatment of this arrhythmia particularly if it occurs as a complication of myocardial infarction and in instances in which intravenous injections of quinidine were considered indicated hitherto Details of dosage and administration of these drugs are given Digitalis which is usually thought to be contra indicated in this arrhythmia can in our opinion be given far more freely than hitherto assumed provided the arrhythmia is not due to the drug in such cases it often abolishes the arrhythmia

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CHAPTER VII

EXTRASYSTOLES AND THE NERVOUS SYSTEM

INTRODUCTORY REMARKS

The part which the nervous system plays in precipitating or modifying ectopic arrhythmias is as important as it is complex Using the words nervous system in their widest sense that is to include the action of autonomic nerves reflexes the central nervous system as well as psychological factors its influence on such arrhythmias in man is so widespread and profound that the resulting clinical importance is obvious Moreover a great deal of experimental evidence on this problem in various animals has been collected under widely varying conditions Taken together such clinical and experimental observations throw some light on the mechanism of extrasystolic and allied arrhythmias and are thus also of physiological interest

The relationship between the nervous system and cardiac arrhythmias had been noticed for a long time and its significance was grossly overrated in the past by some who considered such arrhythmias to be due only to nervous influence The observations that ectopic arrhythmias may occur in the isolated perfused heart and thus independent from central nervous control that electrical stimulation of vagus or sympathetic nerves alone produces such irregularities only exceptionally whilst the opposite effects on the cardiac rhythm may result from the same kind of stimulation of the same nerve according to the conditions of the experiment demonstrate conclusively that no simple relationship obtains It will be seen that in most cases in which nervous influences precipitated extrasystolic and allied arrhythmias with any degree of certainty complex experimental conditions were present which resulted in the heart s being predisposed to the exhibition of the arrhythmia It seems reasonable to postulate a similar predisposition in man to account for the widely varying incidence of such arrhythmias under seemingly similar conditions

ECTOPIC BEATS PRECIPITATED BY DIRECT (FARADIC) STIMULATION OF VAGUS AND SYMPATHETIC

While it was found that occasionally stimulation of the vagus alone (Hering 1909 Lewis 1914a) or sympathetic alone (Rothberger and Winterberg 1911a p 344 1911b p 520 footnote Kure 1913) may elicit ectopic beats this occurrence is exceptional and it soon became obvious that in order for the stimulation of such autonomic nerves to produce ectopic rhythms other conditions present at the same time had to render the heart predisposed for the development of arrhythmias of this kind

One of the earliest of such observations is that of Hering (1901) If in the isolated heart preparation a sudden rise of intra ventricular pressure precipitated by clamping of the cannula permitting the outflow of blood from the ventricle failed to produce extrasystoles simultaneous stimulation of the vagus produced this effect Similarly Weiland found in experiments on rabbits that weak stimulation of the peripheral end of the vagus brought out extrasystoles when clamping of the aorta alone had failed to do so In some of his experiments extrasystoles occurred as a result of dyspnoea or of insufflation of smoke into the nostrils these too became less frequent after bilateral vagotomy and could be made to reappear by vagal stimulation It is important to note that in some of these experiments the

extrasystoles occurred without any noticeable vagal slowing of the normal rate it is clear therefore that the effect of vagal stimulation cannot consist exclusively in the retardation of the normal impulse formation allowing more time for ectopic beats to become manifest The further observation of Weiland s that only weak stimulation of the vagus precipitated extrasystoles whereas strong stimuli had the reverse effect points in the same direction (*See also* Luten below) Hering (1911) emphasized the physiological significance of the fact that the occurrence of extrasystoles was independent of a change of the normal rate

In discussing these observations we have used the term extrasystoles for the heterotopic beats in accordance with the authors of the papers discussed However the question arises whether heterotopic beats of this kind should be considered extrasystoles in the strict sense of the term The nature of extrasystoles and the difference between extrasystoles and automatic beats is discussed in the chapter on Mechanism reasons will there be advanced for our view that those ectopic beats which are not preceded by a precipitating beat at constant time intervals are produced by a different mechanism and should therefore be distinguished as automatic beats from the more passive phenomenon of the true extrasystole

*Similar considerations will have to be applied to the extensive investigations by Roth*berger and Winterberg where a more accurate determination about the origin and nature of the ectopic rhythm is possible since in addition to the mechanical records of auricle and ventricle electrocardiograms were also obtained In their experiments on dogs these authors found that simultaneous stimulation of vagus and sympathetic precipitated beats originating in distal centres in the ventricles Stimulation of the accelerans tended to precipitate impulse formation in the ipsilateral ventricle when at the same time normal impulse formation was inhibited by vagal stimulation In these experiments stimulation of the right vagus usually had a more marked inhibitory effect on the normal pacemaker than that of the left (1911a) Ectopic beats occurred more readily if the animal had previously been given small doses of barium chloride (0 005–0 01 g) with larger doses (0 025–0 05 g) such arrhythmias occurred after stimulation of the left accelerans without simultaneous vagal stimulation (1911b) Calcium chloride had a similar effect though much larger doses (0 1–0 2 g) were necessary but strontium and magnesium were ineffective It was also found that barium chloride did not lower the threshold for stimulation of the accelerans and it was concluded that barium and calcium chloride had a selective sensitizing effect on the impulse forming centres in the ventricles an impressive early example of a predisposition of the heart to develop ectopic rhythms as a result of nervous influence Other instances will be detailed below In Rothberger and Winterberg s records the ectopic beats occurred *in groups without any definite time relationship to the preceding beat normal or ectopic* By diminishing the intensity and particularly the duration of the electrical stimulation it was possible occasionally to precipitate single extrasystoles The arrhythmias observed in such experiments would in our opinion more appropriately be considered to be due to increased automatism of a ventricular centre or centres than to consist of extrasystoles Lewis (1914b) had already expressed doubts whether the arrhythmias experimentally produced by Rothberger and Winterberg and extrasystoles have the same genetic origin and subsequent work has tended to substantiate such doubts

In a similar manner chloroform (Levy) and cyclopropane (Allen Stutzman and Meek) were found to sensitize the heart in such a manner that subsequent stimulation of the sympathetic elicited ectopic arrhythmias The latter drug seems to have predisposed the heart to various arrhythmias on manipulation of the vagus though extrasystoles were observed in only three out of thirty six operations (Freeman) During operations involving section or isolation of the gastric vagi premature beats were found only rarely in clinical and experimental (dogs) observations (Gullickson McRae and Campbell) This will be discussed in the appropriate sections of the chapter on Drugs (pp 301 304)

There can be no doubt however that true extrasystolic arrhythmias were produced by vagal stimulation in dogs after aconitine administration (Scherf 1929) In these experiments an amorphous preparation was used (0 5 or 1 0 g in 100 cc of distilled water acidified) and the degree of intoxication carefully adjusted individually in each experiment If such small doses were employed that alone failed to produce any noticeable change in the rate or rhythm of the heart faradic stimulation of the vagus right or left invariably produced a bigeminal rhythm or multiple extrasystoles arising in the same focus The extrasystoles usually were ventricular in origin arising in the left ventricle more frequently than in the right they started immediately with the vagal stimulation The extrasystoles of the bigemini were accurately coupled to the preceding beats and had constant shape in the electrocardiogram

Fig 156 provides an example of such an experiment The right vagus was stimulated by a weak faradic current after the first normal beat occurred Each automatic (escaped) beat occurring during vagal stimulation was followed by a group of four ventricular extrasystoles the first of which was accurately coupled to the automatic beat (coupling 0 32 second) The extrasystoles persisted after the end of vagal stimulation for various periods of time in some experiments for several hours depending amongst other conditions of the experiment on the degree of aconitine intoxication If the extrasystoles had subsided renewed vagal stimulation caused them to recommence If extrasystoles were already present as a result of the administration of aconitine stimulation of the vagus invariably increased their number and precipitated multiple extrasystoles or short runs of paroxysmal tachycardia Atropine abolished the extrasystoles in certain stages of aconitine intoxication Choline and choline derivatives as well as potassium chloride had the same effect as vagal stimulation choline remaining effective even with full atropinization

Conversely short faradic stimulation of the sympathetic (accelerans) or as unpublished experiments showed injection of small doses of adrenaline abolished the extrasystoles after a short latent interval and at a time before the ensuing tachycardia would itself be likely to have this result Calcium chloride (1–5 cc of a 10 per cent solution) had a similar effect

In a minority of the experiments auricular extrasystoles occurred at times as auricular bigemini Vagal stimulation had essentially the same effect on auricular as on ventricular extrasystoles with the important difference that whereas the ventricular extrasystoles occurred immediately at the onset of vagal stimulation the auricular ones did so shortly after the end of stimulation if auricular extrasystoles were present as the result of aconitine alone they temporarily disappeared during vagal stimulation reappearing in increased numbers shortly after the end of stimulation During vagal stimulation the inhibitory action on the auricles prevented the appearance of the extrasystoles

These findings are of interest from various points of view First of all the combination of aconitine with vagal stimulation was the first method which made it possible with a great degree of certainty experimentally to reproduce bigeminal rhythm due to ventricular extrasystoles with constant coupling It is a surprising fact that this kind of arrhythmia so common in man can only with great difficulty be produced in animals The few other methods known to produce this form of bigeminal action are discussed on p 194 The importance of being able to study in experiments an arrhythmia which is such a frequent occurrence in man is obvious Furthermore the experiments discussed are one of the very few instances demonstrating a direct vagal effect on the ventricles of the mammalian heart which generally does not seem to exist (Drury Rothberger and Scherf) Moreover the more recent observation (Scherf and Chick) that the topical application of acetylcholine to the ventricles of dogs precipitated ectopic ventricular rhythms and that the same procedure in atropinized dogs caused ventricular tachycardia illustrates a further mechanism which may account for or contribute to this finding it establishes that acetylcholine may precipitate ectopic rhythms

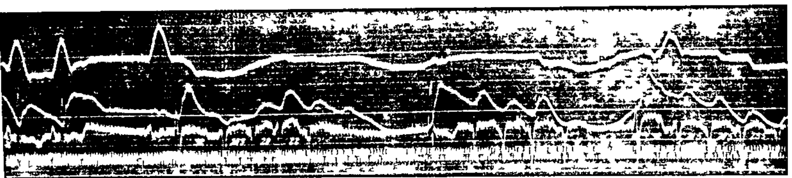


Fig 156.—From an experiment on a dog Records from above downward suspension record of right auricle of right ventricle electrocardiogram (ano oesophageal lead) time base 0 02 second Stimulation of the right vagus precipitates multiple ventricular extrasystoles after sensitization with aconitine The beginning of the (faradic) stimulation is recognizable in the figure (in the second P wave) by the slight distortion of the electrocardiogram produced by the faradic current From Scherf 1929 *Z ges exp Med*

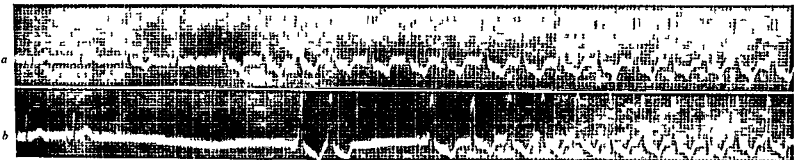


Fig 157.—From an experiment on a dog Top record regular ventricular tachycardia elicited by the topical application of a 30 per cent solution of sodium chloride on the right ventricle Bottom record Ventricular tachycardia precipitated by vagal stimulation The bottom record was obtained after the top record For further explanation see text From Piccione and Scherf *Bull N Y med Coll*

It is also significant that in those particular experimental conditions vagal stimulation had the effect of enhancing ectopic impulse formation in the ventricles while having the usual inhibiting effect on the higher centres of impulse formation This opposite effect of stimulation of the same nerve on the various centres also proved for the sympathetic is of considerable physiological importance regarding the mechanism of impulse formation (*See* Scherf 1929 also the chapter on Mechanism of Origin of Extrasystoles) Furthermore the sympathetic is known not only to have a direct effect on the mammalian ventricle but there to facilitate the onset of ectopic rhythms so that the described effect of stimulation of the sympathetic in abolishing extrasystoles is the reverse of that observed in many other experimental conditions A further instance of this kind is the suppression by sympathomimetic compounds given intravenously of ventricular ectopic tachycardias elicited in dogs by the topical application of aconitine (Charlier and Klutz)

Ventricular ectopic beats were also elicited by vagal stimulation in dogs after injection of digitalis (Kobacker and Scherf) The rate of the ectopic rhythms appearing during and shortly after stimulation of the vagus was slightly higher than that of the prevailing sinus rhythm

That stimulation of the vagus on the one hand and of the sympathetic on the other need not always have the opposite effect in producing and abolishing respectively extrasystolic arrhythmias was shown by Piccione and Scherf in experiments on extrasystoles caused in the dog by the application of hypertonic solutions of sodium or barium chloride on the cardiac surface or by subepicardial injections If tachycardias thus produced had subsided spontaneously faradic stimulation of the sympathetic particularly of the right stellate ganglion brought them out again and their rate increased markedly But the abnormal beats also re appeared if the vagus was stimulated In some cases the latter phenomenon may simply have been due to the slowing of the normal rhythm which facilitated the occurrence of ectopic ventricular beats Not rarely however a ventricular tachycardia which had disappeared could be brought out again for a period of three to four minutes by stimulation of the right or left vagus and on these occasions the rate of the tachycardia was faster than that produced by the previous chemical irritation alone without vagal stimulation This would appear to be another of the few instances pointing to a direct effect of the vagus on the mammalian ventricle

Fig 157 was obtained from such an experiment A subpericardial injection of 0 1 cc of a 30 per cent solution of sodium chloride in the conus area of the right ventricle was followed by a ventricular tachycardia (Fig 157a) The rate of the sinus rhythm was 115 and that of the tachycardia was 162 Two minutes later the tachycardia had disappeared At this stage the right vagus was faradically stimulated (Fig 157b) with the effect that a prolonged standstill of the heart occurred which was interrupted by two beats originating in the same area as the extrasystoles which followed the injection of sodium chloride After a second shorter interval (stimulation of the vagus continuing) paroxysmal tachycardia with a rate of 180 and again originating in the same focus occurred Since by repeating vagal stimulation after a few minutes short bouts of the same tachycardia could be elicited again the assumption seems reasonable that such spells of tachycardia were not a coincidence A short bigeminal rhythm also could be precipitated by vagal stimulation in some of these experiments

In dogs following the intravenous administration of thiobarbiturates ventricular extrasystoles appeared during vagal stimulation even if they had been absent before (Gruber)

Fig 158 demonstrates two auricular extrasystoles originating in different foci following prolonged faradic stimulation of the right vagus in a dog anaesthetized with nembutal (without any other drug) The stimulation of the right vagus was repeated six times and one or two auricular extrasystoles appeared after each stimulation

These examples illustrate how complex the action of stimulation of vagus and

sympathetic is in its effect on extrasystolic and allied arrhythmias According to the circumstances of the experiment the kind of animal and anaesthetic used and the kind of drug employed in order to sensitize the centres of ectopic impulse formation stimulation of the same nerve may have quite different and at times opposite effects It is also evident that stimulation of the cardiac nerves alone produced extrasystolic and allied arrhythmias only in a small minority of cases and that in all those experiments in which such arrhythmias followed stimulation of these nerves with any degree of certainty the heart had been rendered in a special condition predisposing it for the development of ectopic arrhythmias

At this juncture the fact should be stressed that results obtained in experiments on rabbits should only be used with special reserve for the analysis of the mechanism of such arrhythmias in other animals and man since ectopic arrhythmias are apt to occur especially easily in the rabbit particularly if morphine which is known to favour their occurrence was used as an anaesthetic (Kure 1913 Hering 1915)

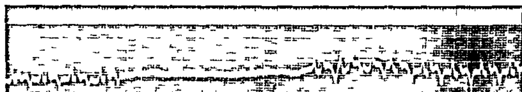


Fig 158 —From an experiment on a dog Two auricular extrasystoles following prolonged faradic stimulation of the right vagus

ECTOPIC BEATS PRECIPITATED BY WAY OF REFLEX FROM THE CAROTID SINUS AND THE PART PLAYED BY THE PRESSO RECEPTOR NERVES

Some relevant observations dating from long before the discovery of the function of the carotid sinus and of the action of presso receptor nerves may briefly be quoted Thus Cyon (quoted from Koch) found in 1898 that stimulation of the depressor nerve abolished bigeminal heart action even if the lowering of blood pressure was negligible This was subsequently confirmed by Hering (1922) Irregular heart action in rabbits as a result of clamping the carotid arteries was reported by Sewall and Steiner as early as 1885 and later by Hirsch and Stadler with experimentally produced aortic incompetence after severing of the depressor nerves Kisch who studied such arrhythmias more closely using however only a record of the blood pressure for their analysis interpreted them as extrasystoles and found that their occurrence was facilitated by simultaneous dyspnoea stimulation of the central end of the vagus or of the superior laryngeal nerve and that they persisted after bilateral vagotomy or atropinization A better understanding of the mechanism of such arrhythmias became possible only after the discovery by Hering of the carotid sinus as a site of origin of reflexes Hering (1927) himself added the observation that stimulation of the carotid nerve abolished arrhythmias produced by clamping the carotid arteries and that just as in the case of the depressor nerve this effect was independent of a change in blood pressure Heymans (1929) (quoted from Regniers 1930) noticed the occurrence of extrasystoles when the pressure in the carotid sinus fell to 70–80 mm Hg

Such arrhythmias elicited by clamping of the carotid arteries were subsequently studied by means of electrocardiograms Regniers found that ectopic beats occurred singly as well as in groups that they originated from various foci and that paroxysmal tachycardia as well as A V nodal rhythm may occur in such circumstances He confirmed that such arrhythmias persisted after both vagi had been severed but they could be abolished by ergotamine Schott found also in rabbits that ectopic rhythms elicited by clamping of the carotid

arteries occurred more readily if the animals had been sensitized with barium chloride aconitine or strophantin given in doses which alone did not produce any changes in heart rate or rhythm In some experiments with barium long chains of bigeminal heart action with constant coupling and constant shape of the extrasystoles in the electrocardiogram could be produced (Fig 159) the arrhythmia immediately disappearing on releasing the carotids to reappear on renewed clamping—another of the few methods experimentally to produce this arrhythmia Severing of both depressor nerves facilitated the occurrence of arrhythmias resulting from clamping of the carotid arteries (Hering 1925 Regniers 1929 Schott) This was to be expected in view of the synergistic action of depressor and carotid sinus nerves By removing their compensating action severing of the depressor nerves will enhance the effect of reducing the physiological stimulus of the carotid sinus nerves which results from clamping of the common carotid arteries In such experiments it was also found that stimulation of the intact vagus may precipitate the occurrence of extrasystoles as well as abolish them (Schott) Similarly Danielopolu Marcou and Proca reported that stimulation of the carotid sinus in dogs or cats sensitized by means of ligatures in the myo cardium or of small branches of the coronary arteries or by means of intravenous injections

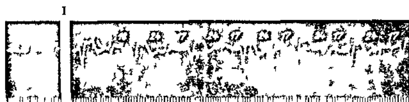


FIG 159 —From an experiment on a rabbit Lead 2 Time base 0 02 second After 5 mgm of barium chloride given intraperitoneally The beginning of the tracing shows sinus rhythm After clamping of both carotid arteries marked I bigeminal rhythm Note accurate coupling and constant shape of the ventricular extrasystoles From SCHOTT *Pflüg Arch ges Physiol*

of calcium or barium chloride or strophanthin may precipitate as well as abolish ectopic rhythms Dikshit (1934b) found in cats that sodium barbitone given intracerebrally or intravenously lessened or abolished cardiac arrhythmias elicited by clamping of the carotid arteries

It can therefore be said that stimulation of the presso receptor nerves tends on the whole to prevent or abolish ectopic rhythms whereas elimination of their action (severing of the depressor and/or sinus nerves lowering of the pressure in the sinus by clamping the com mon carotid arteries) has the opposite effect It must be borne in mind however that the reverse of this usual effect may be observed depending *inter alia* on the rhythm prevailing at the time of the experimental interference on such nerves

These experimental findings accord well with the observations that pressure on the caro tid sinus in man may precipitate as well as abolish ectopic beats Rihl (1912) found that pressure on the vagus elicited extrasystoles but as he used only mechanical records in some observations only cubital pulse tracings his results cannot be analysed in any detail Hering (1911) also reported that pressure on the vagus in man can increase the number of extrasystoles (*see also* Kleemann) particularly in the period following the pressure

Later Rihl (1929) described two cases in which carotid pressure provoked ventricular extrasystoles which in the electrocardiogram had the same or almost the same shape as those occurring spontaneously In both extrasystoles had started as a result of digitalis but in one of them no digitalis had been given for ten days Digitalis extrasystoles with fixed

coupling but arising from various foci produced by vagal pressure and not associated with any material change in the auricular rate had been described previously by Weil

Fig 160a shows a ventricular extrasystole which occurred during carotid sinus pressure applied for terminating an attack of auricular paroxysmal tachycardia Observations of this kind are fairly common

Not only single but also multiple ventricular ectopic beats may occur during carotid sinus pressure Fig 160b provides an example obtained in a fifty four year old woman complaining of palpitation The tracing shows right bundle branch block as a result of pressure on the right carotid sinus multiple ventricular ectopic beats were recorded and this *observation could be repeated at short intervals It was made in the same patient whose* record is reproduced in Wenckebach and Winterberg s monograph (Fig 190 on plate 80), and it was also observed that pressure on the right vagus precipitated a ventricular tachycardia with a rate up to 278 which moreover could be abolished by the same manoeuvre which elicited it

Meredith and Beckwith reported two cases in which ventricular tachycardia was recorded during carotid sinus pressure applied for stopping an attack of paroxysmal supraventricular tachycardia

The observation quoted earlier in this chapter that topical application of acetylcholine may precipitate ectopic ventricular rhythms in the dog may well have a bearing on the mode of origin of such ectopic arrhythmias occurring during carotid sinus pressure

Regarding such arrhythmias arising in the *auricles* auricular extrasystoles paroxysmal auricular tachycardia auricular flutter and fibrillation have been described following carotid sinus pressure (Aalsmeer Mandelstamm Blumenfeld Schaeffeler and Zullo) Fig 160c shows two ectopic auricular beats which were recorded during pressure on the right carotid sinus applied to terminate an attack of supraventricular tachycardia

On the other hand carotid sinus pressure may also suppress extrasystoles This is easily understood in the case of *auricular* ones as impulse formation in the auricles is known to be largely under vagal control Thus Luten reported a carefully analysed case in which auricular extrasystoles disappeared soon after injection of atropine (grain 1/30) at a time when the sinus rate was slowed as a result of the initial vagal stimulation With the subsequent tachycardia in the vago paralytic stage of the atropine effect the ectopic beats became more and more numerous Apart from the effect of atropine the extrasystoles disappeared as a result of vagal pressure but the effect was not constant This observation demonstrates that at least in some cases vagal tone is a far more important factor in determining the occurrence of extrasystoles than the length of the diastolic interval

There can also be no doubt that in some cases carotid sinus pressure may suppress *ventricular* extrasystoles (Kleemann Kaufmann and Rothberger) and tachycardias (Wenckebach and Winterberg) This observation was difficult to understand at a time when pressure in the neck was assumed to produce a direct mechanical stimulation of the vagus As it is now known that stimulation of the presso receptor nerves results not only in an increase of vagal but also in a decrease of sympathetic tone this latter effect may reasonably be assumed to be the cause of the disappearance of ventricular extrasystoles as a result of carotid sinus pressure The paramount importance of efferent sympathetic pathways in such reflexes has been demonstrated in a great variety of experimental conditions By recording in cats the sympathetic impulses in one of the small nerves running from the stellate ganglion to the heart Bronk Ferguson and Solandt found that increase in the pressure within the carotid sinus results in a decrease of the sympathetic impulses amounting to temporary complete inhibition if the pressure was raised to 125–150 mm Hg The duration of this inhibition depended on the height of the pressure in the sinus and was often increased by section of both the aortic depressor nerves

The effect of direct mechanical stimulation by pinching with a pair of forceps of the

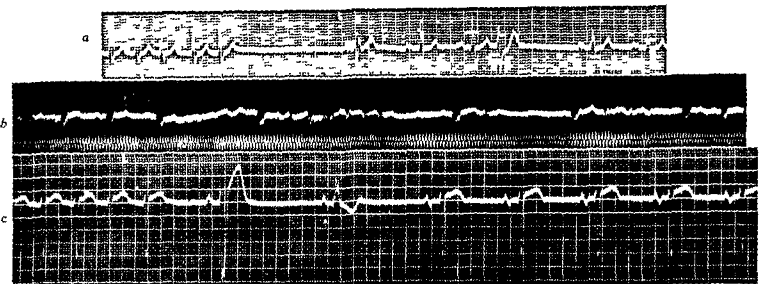


FIG 160—*a* A ventricular extrasystole occurring during carotid sinus pressure which terminates an attack of paroxysmal auricular tachycardia *b* Lead I Multiple ventricular ectopic beats during carotid sinus pressure The two records were obtained from different patients *c* Lead V 1 Two ectopic auricular beats with aberrant intra ventricular conduction recorded during pressure on the right carotid sinus Note the difference in shape of the P waves of these two beats indicating either different site of origin or intra auricular disturbances of conduction Both differ from the diphasic P waves of the subsequent sinus beats

carotid sinus in man was studied by Hill in twenty patients in whom the region was exposed for operation Only in the two cases in which chloroform was used as anaesthetic were ventricular extrasystoles recorded here they tended to occur as bigemini the extrasystoles being only slightly premature The arrhythmia was not accompanied by a significant variation in the heart rate and closely resembled that arising spontaneously under chloroform anaesthesia

It is thus obvious that carotid sinus pressure in man may precipitate as well as abolish extrasystoles Hering (1925) pointed out that this seemingly contradictory result may be due to the exact site at which the pressure is applied if the sinus itself is compressed it results in a stimulation of the sinus nerve via the mechanical stimulation of the carotid sinus whereas if the pressure is applied below the sinus the common carotid artery is compressed whereby the blood pressure within the sinus is reduced and the opposite effect on the sinus nerve namely decrease of the physiological stimulus is produced But Hering himself admitted that such a sharp distinction between the two points of compression often is not possible with compression below the sinus a mechanical effect may be produced on the sinus by traction and in subjects with short and obese necks it may be altogether impossible accurately to localize the site of pressure While in the clinical experiment the exact site of the pressure is of course of importance no such considerations arise in connexion with animal experiments In our view the observation that the same procedure may have the opposite effect on the heart rhythm is only one of many similar instances well known in physiology that the effect of direct as well as reflex stimulation of nerves depends *inter alia* on the condition of the organ supplied by the stimulated nerve

A few examples The effect, upon the stomach of cats of vagal stimulation was found to be dependent only on the condition of the organ the atonic stomach responded by contraction the hypertonic one by relaxation (McSwiney and Wadge) Similar conditions were found by McCrea and McSwiney regarding the effect upon the pylorus and fundus of the cat s stomach of stimulation of the hepatic branch of the vagus The effect upon the uterus of stimulation of the hypogastric nerve differs according to the presence or absence of pregnancy (Langley and Anderson)

Regarding the effect of nervous stimulation by way of reflex independent of the site of stimulation the excitation tends to favour stretched muscles (v Uexkull Sherrington Magnus) and is thus dependent on the conditions in the periphery (Bethe) In decerebrate cats pressure on the hard palate produces by way of reflex opening of the jaws if the mouth was shut bu their clenching if the mouth was open In man a flexor reflex can in certain circumstances depending on the situation as a whole be converted into an extensor one (Bethe and Fischer) (For ref of the papers quoted in the last two paragraphs see Schott)

It seems to us that the condition of the heart and particularly its rhythm at the time is one of the main factors determining whether stimulation of the presso receptor nerves results in precipitating or abolishing ectopic arrhythmias

In a similar way as with carotid sinus pressure extrasystoles were occasionally seen during or following pressure on the eye bulb (Aschner Dagnini reflex) (Jenny Ferralis and Pezzi Danielopolu *et al* 1925) Pruche stated however that he found extrasystoles only in cases in which they had been present before ocular pressure was applied Sabena and Posteli examined electrocardiographically the effect of ocular pressure in fifty patients and amongst other variations in heart rate and rhythm found extrasystoles of several kinds namely auricular ventricular and polymorphic No tracings are however reproduced in their paper Landman and Ehrenfeld reported an observation in which eyeball pressure was thought to have precipitated short runs of ventricular fibrillation but in our opinion the reproduced tracings demonstrate short paroxysms of multiform ventricular extrasystoles

Roth reported an observation on an eighteen year old man with angioneurotic oedema in which ocular pressure produced extrasystoles if adrenaline (1 mg) had been injected previously The analogy of this clinical observation with the experimental findings of Rothberger and Winterberg that combined stimulation of vagus and sympathetic may produce ectopic arrhythmias is obvious

ECTOPIC BEATS DUE TO REFLEXES FROM THE RESPIRATORY TRACT

Cardiac arrhythmias resulting by way of reflex from chemical irritation of the nasal mucous membrane have been known since Kratschmer s investigations on rabbits in 1870 Using a variety of chemical irritants amongst them chloroform ammonia and tobacco smoke and recording the blood pressure in the carotid he found gross irregularities and slowing of the heart action If the irritant was applied after bilateral vagotomy a curious intermittency of the heart beat was sometimes noticed akin to Traube s *pulsus bigeminus* This never occurred at the time of application of the irritant but only after a longer latent interval and such arrhythmias recurred without the stimulus being reapplied Destruction of the sympathetics and depressor nerves as well as severing of the olfactory nerves did not affect the arrhythmias but section of the trigeminal abolished them

Much of this early work has sub equently been confirmed and amplified Knoll (1872) studying in detail the *pulsus bigeminus* under the conditions in which Kratschmer found it to occur observed that its duration equalled that of two normal cycles a finding that should later prove of such decisive importance for the accurate analysis of extrasystolic arrhythmias He also clearly recognized that the *pulsus bigeminus* and *trigeminus* were caused by the premature occurrence of beats which fell so early in diastole that the filling of the heart was inadequate At first such arrhythmias were attributed to the concomitant rise in blood pressure (Knoll Heidenhain) which it was thought by Heidenhain acted on the intracardiac ganglia Later investigations by Knoll (1897) however showed that such arrhythmias occurred independently of a rise in blood pressure and confirmed that they persisted after bilateral vagotomy atropinization and removal of the lower cervical and upper dorsal ganglia The methods available at that time were inadequate for a reliable analysis of the kind of arrhythmia but in view of subsequent observations the assumption seems well justified that they consisted largely of ectopic arrhythmias and extrasystoles as stated by Hering (1900 1901)

Koblanck and Roeder starting from Koblanck observation that arrhythmias could be elicited in man by stimulation of certain areas in the nose investigated this problem in dogs and rabbits It was found that arrhythmias could be produced by stimulation of a circumscribed area on the posterior part of the nasal septum opposite the middle turbinate whereas stimulation of other areas was ineffective The irregularities seem to have consisted of single or multiple extrasystoles and short periods of bigeminal heart action bilateral vagotomy suppressed the arrhythmias temporarily but bilateral resection of the trigeminal abolished them However the experimental technique employed by these authors was so inadequate that it was repeatedly criticized

Magne Mayer and Plantefol also found arrhythmias and bradycardia resulting from stimulation of the upper air passages by irritant vapours but that of the trachea and bronchi greatly differed in its effect on the respiration and no material effects on the cardiac action were observed As only pulse and blood pressure tracings were recorded no detailed analysis of their results is possible

As far as the bradycardia is concerned which occurs in rabbits as a result of the insufflation of irritating vapours into the nostrils Brucke conclusively demonstrated in 1917 that the efferent mechanism consists not only of a stimulation of the vagi but also—at least in certain animal —of an additional inhibition of the sympathetics

More recently this problem was extensively re investigated by Allen (1930–33) Arrhyth mias (*pulsus bigeminus*) were found to result in rabbits particularly easily from insufflation of benzol and could also be produced by stimulation of the central end of the cut vagus but not by faradic or mechanical stimulation of the peripheral end of vagus depressor and cervical sympathetic or of the lateral wall of the nostrils No constant relationship between the onset of bigeminal pulse and height of blood pressure was found and the arrhythmias occurred even if a rise in blood pressure was prevented by an equalizer by ergotamine or transection of the spinal cord in the midthoracic region they were also independent of the carotid sinuses (1930b) The afferent pathway was found to be the trigeminal though the olfactory nerves may also have some part (1930a) The impulses descend the median half of the lateral columns of the spinal cord and pass to the left ventricle by way of the upper thoracic roots and the stellate ganglia (1931a) The arrhythmias were abolished by section of the lower cervical cord or removal of the stellate ganglia The central connexions of this reflex are discussed below (p 267) While it seems fairly certain that the arrhythmias studied by Allen were extrasystolic in origin only very few electrocardiograms are reproduced and the diagnosis of the disturbances of rhythm is mainly based on carotid blood pressure tracings No finer analysis of the arrhythmias is therefore possible in particular no con clusions can be drawn about the focus of origin of the ectopic beats Owing to the inertia of the recording system employed not even a tentative explanation can be given of the nature of changes in the arrhythmia which were observed in some experiments Moreover the results about the relationship between rise of blood pressure and onset of premature beats were inconclusive

A few words here may not be amiss to clarify our attitude toward work on arrhythmias in which only mechanical records of blood pressure and/or arterial pulse tracings were obtained Much is owed to work of this kind which showed under what conditions arrhyth mias occur and by what interferences they are modified prevented or abolished The pres ence of ectopic beats and extrasystoles may be inferred from such records with a certain degree of probability particularly if additional mechanical tracings of auricular activity or preferably electrocardiograms were recorded in at least a certain proportion of experiments We should like to emphasize however that no reliable analysis of the underlying arrhyth mias is possible on the strength of arterial pulse or blood pressure tracings as these fail to give any information about auricular activity which is indispensable for analysis A great variety of mechanisms may for instance result in a *bigeminal pulse* as is discussed in the appropriate chapter (p 204) Moreover with a mechanical pulse tracing or the usual blood pressure record the inertia of the recording system results in such marked distortions of the record in shape and in time that not even the fundamental distinction between distur bances of impulse formation (ectopic beats extrasystoles) and disturbances of conduction can be made In order accurately to analyse arrhythmias either electrocardiograms or records of ventricular *and* auricular activity obtained with adequate recording systems or both have to be postulated For these reasons the value of some otherwise important work is limited if a detailed analysis of the arrhythmias is the object in view

While as already mentioned Magne Mayer and Plantefol failed to find any cardiac effect of *chemical* stimulation of the lower respiratory passages Reid and Brace showed that extrasystolic and other arrhythmias occurred in ten out of thirty five patients anaesthetized with cyclopropane or nitrous oxide and oxygen as a result of *mechanical* irritation of the trachea by inserting a tracheal tube inflation of a Waters cuff spraying of the throat or introduction of a bronchoscope Auricular as well as ventricular extrasystoles were re corded *the latter sometimes arising from various foci* A possible anatomical basis for such reflexes is contained in the findings of Sunder Plassmann who demonstrated in the wall of the bronchi receptors resembling those in the carotid sinus marked slowing of the heart was shown to follow mechanical stimulation of such areas These findings are of

practical importance as they demonstrate the need for caution in applying mechanical stimuli to the trachea or bronchi especially in light anaesthesia cyclopropane seems particularly apt to sensitize the heart in this respect

Amongst the arrhythmias complicating total pneumonectomy extrasystoles formed only a small fraction (Massie and Valle)

Regarding the effect of respiration on the incidence of extrasystoles Busquet observed in the dog that they were more frequent during expiration and attributed this to the slower heart rate Owing to the rather primitive method used no more detailed analysis of the arrhythmia is possible

Ventricular and auricular extrasystoles as well as auricular flutter and fibrillation precipitated by *deep breathing* have been repeatedly described (Stokes Smith and Moody Burak and Scherf) Evans investigated the effect of deep inbreathing on lead 3 in two hundred healthy adults and found that in one case deep inspiration always induced a short bout of paroxysmal tachycardia in five instances extrasystoles appeared with deep inspiration while in three they disappeared having been present in lead 3 taken during ordinary respiration In Case 3 of the series of Smith and Moody deep breathing caused paroxysmal auricular fibrillation only when the patient was apprehensive whereas after his fears had been dispelled deep breathing produced only extrasystoles an interesting example showing the interaction of several predisposing factors in producing various arrhythmias In another of their cases (Case 2) return extrasystoles followed deep breathing

Extrasystoles occurring as a result of forced expiration against the closed glottis (Valsalva s experiment) are at least partly due to reflexes Thus Burger found extrasystoles following the rise in intrapulmonary pressure thus produced in fifteen amongst 145 subjects and attributed these and other changes in the electrocardiogram to a vagal effect which under such conditions outlasts the increase in sympathetic tone after the end of the effort

Forssman and Stenqvist reported an unusual observation in a man of thirty six without cardiac disease This individual was able to produce attacks of paroxysmal tachycardia by deep inspiration by pushing forward his abdominal wall without straining and while holding his breath and subsequently also by Valsalva s experiment Carotid sinus pressure ergotamine tartrate or prostigmine had no effect on the tachycardia As the result of quinidine (2 grammes daily) the ability to produce such arrhythmias disappeared

During voluntary respiratory arrest cardiac inhibition has been described (Scherf 1945) this phenomenon may however be a central effect

ECTOPIC BEATS DUE TO REFLEXES FROM THE GASTRO-INTESTINAL TRACT

The effect on the cardiac rate and rhythm of reflexes originating in the gastro intestinal tract has been known for a long time and in its extreme degree was demonstrated by Goltz s classic experiment on the frog in which he showed cardiac standstill to follow a blow on the abdomen Engelmann found in experiments on the effect upon the frog s heart of direct stimulation that subthreshold stimuli became effective as a result of faradic stimulation of stomach or intestines which he attributed to a sensitization of the heart due to reflex vagal stimulation Clinically the importance of gastro intestinal maladies on the rhythm of the heart had at certain times if anything been overrated reference has already been made to Solano s and Laennec s view that intermittent pulse was a sign of impending diarrhoea (Historical Remarks)

Ectopic arrhythmias precipitated from the mouth pharynx and oesophagus seem rare but have been reported Thus Medvei and Uiberall reported that following an attack of tonsillitis in a woman of sixty four Adams Stokes attacks occurred on swallowing During such attacks marked bradycardia with occasional extrasystoles (which seem to have been accurately coupled) and sometimes nodal rhythm was found and such attacks could be

precipitated by touching the left faucial pillars or the pharyngeal aspect of the tongue on the left The attacks were abolished by application of radium to the left tonsillar region Extra systoles and short attacks of paroxysmal tachycardia produced by swallowing were reported by Sakai and Mori Wenckebach and Winterberg Gallavardin and Froment (two cases) Forsberg In this connexion reports of the occurrence of Adams Stokes attacks due to swallowing are also relevant as they not only show a reflex effect upon the heart rhythm of swallowing but in some cases they were associated with ectopic impulse formation Thus Flaum and Klima reported a case of a sixty three year old man in whom swallowing induced Adams Stokes attacks the electrocardiogram showed complete standstill up to 5 minutes 28 seconds *interpreted as sino auricular block During the long intervals of standstill* automatic beats occurred partly of A V partly of ventricular origin Such attacks could invariably by produced by touching the superior laryngeal nerve in the left pyriform fossa or at its passage through the hyothyroid membrane whereas carotid sinus pressure was without effect Reiniger in discussing what appears the same case mentioned that ventri cular extrasystoles occurred before the attacks disappeared during paroxysms to reappear when the original rhythm was restored the extrasystoles having various forms and varying coupling Weiss and Ferris reported the occurrence of Adams Stokes attacks on swallowing in a sixty four year old man which originated from a traction diverticulum of the oeso phagus such attacks could be precipitated by distending the diverticulum by means of in flating a balloon inserted into it The electrocardiogram showed complete heart block dur ing the attacks epinephrine and ephedrine while not preventing the block so increased automatic impulse formation that a regular ventricular rhythm ensued the rate of which was sufficiently high to prevent the onset of symptoms The afferent path of the reflex at least in some of such cases is believed to pass through the superior laryngeal nerve

Arrhythmias following experimental distension of the stomach seem first to have been reported in 1872 by Mayer and Pribram but were found only in a minority of the experi ments Subsequent studies confirmed that the occurrence of arrhythmias under such con ditions is by no means constant and rather the exception Thus Burgess Scott and Ivy found periodically recurring premature beats on distension of the stomach in only one out of twelve dogs and Owen obtained extrasystoles only rarely upon distending the viscera in anaesthetized dogs Pearcy and Howard found extrasystoles on distension or squeezing of various viscera in dogs which were sensitized with barium or digitalis In such experiments the anaesthetic employed and the kind of animal used are of paramount importance

In man the occurrence of extrasystoles after a heavy meal is a common occurrence and other conditions producing a displacement upwards of the diaphragms also frequently precipitate such arrhythmias for example pregnancy

Kaestner reported numerous ventricular extrasystoles in a fifty nine year old man with a hiatus hernia They invariably occurred immediately after assuming the supine position and then disappeared

Clinical observations testify to the intimate relationship between gall bladder and heart action Here again however experimental investigations gave inconclusive results Schrager and Ivy saw skipped beats in only one out of five dogs on distending the biliary passages According to Crittenden and Ivy icterus in unanaesthetized dogs seemed to facilitate the onset of cardiac arrhythmias including ectopic beats on distension of the biliary passages The cardiac manifestations however were primarily associated with pain vomiting or retching and were abolished by atropine

In man reports of carefully investigated cases are few Straus and Hamburger found extrasystoles disappear after cholecystectomy in two cases in one of these normal rhythm was found 105 minutes after the operation which tends to support the assumption that the arrhythmia had been due to a reflex from the diseased gall bladder as any toxic effect could hardly have disappeared in so short a time In a third case extrasystoles disappeared

temporarily in the same patient after each of two operations for duodenal ulcer and periduodenal adhesions respectively In yet another case auricular extrasystoles and flutter became more marked after cholecystectomy The authors emphasize that three out of those four patients were neurotic another instance of several factors being present to sensitize the heart Another impressive example of the effect of a diseased gall bladder on cardiac function is provided by the first case of a series of six published by Fitz Hugh and Wollerth In this patient suffering from nocturnal pain in the precordium and left shoulder in addition to violent attacks of epigastric and right upper quadrant pain the electrocardiogram showed signs of myocardial damage with numerous ventricular extrasystoles six weeks after cholecystectomy the tracing was entirely normal and the extrasystoles had disappeared

Reports about the occurrence of extrasystoles as a result of handling abdominal viscera at operations in man are conflicting Bettmann and Rubinfeld saw ectopic beats during cholecystectomy performed under spinal anaesthesia in only two out of sixteen patients Wakefield found extrasystoles frequently (together with other electrocardiographic changes) when traction was made on the gall bladder or when it was distended with normal saline solution The effect of major abdominal operations on the cardiac rhythm was studied electrocardiographically by Maher and collaborators In eighty nine operations (in which ether or nitrou oxide was used) extrasystoles were found in thirteen cases (auricular in five ventricular in four nodal in two and auricular and ventricular in two) only in ten instances was the occurrence of the arrhythmia related with certainty to a definite operative procedure for example stretching the mesentery pulling the gall bladder or omentum or palpating a neoplasm

CENTRAL NERVOUS SYSTEM—BRAIN—AND ECTOPIC BEATS

A G Levy s extensive work on the occurrence of extrasystoles in cats under light chloroform anaesthesia was the starting point of important investigations demonstrating the part played by certain areas in the brain in the production of such arrhythmias Levy himself demonstrated that when epinephrine was injected intravenously into cats under light chloroform anaesthesia extrasystoles and ventricular fibrillation ensued within a few seconds and that this effect was still present in pithed cats with the brain destroyed

Stimulation of the central end of the vagus also may precipitate extrasystoles in cats under chloroform anaesthesia (Brow Long and Beattie Dikshit 1934a)

Further progress was made by the detailed investigations of Brow Long and Beattie starting from the chance discovery that such extrasystoles in lightly chloroformed cats were abolished or prevented by decerebration at the Sherrington level It was found that a centre or centres exist in a certain region in the brain stem the removal of which resulted in the abolition of the extrasystoles the area having the following boundaries anteriorly and superiorly a line joining the anterior edge of the superior colliculi to the posterior edge of *the optic chiasma posteriorly a line joining the anterior edge of the superior colliculi to* the posterior edge of the mammillary bodies laterally an imaginary plane not more than 3 or 4 mm from the medial sagittal plane Stimulation of this region was found to produce extrasystoles when they were not already produced by chloroform Moreover stimulation of certain points of the hypothalamus produced extrasystoles one such point was close to the entrance of the aqueduct of Sylvius into the third ventricle another one about 3 mm above and slightly posterior to the origin of the infundibular recess Degeneration experiments showed tracts partly passing into the *formatio reticularis* of the brain stem and partly into the intermedio lateral columns of the grey matter in the thoracic and upper lumbar parts of the spinal cord It was concluded that the occurrence of extrasystoles resulting from stimulation of the above region of the hypothalamus was due to stimulation of the general sympathetic pathways as well as of the paths controlling the secretion of adrenaline for it

was found that stimulation of the hypothalamus still produced extrasystoles after the removal of the suprarenals

Blocking or interruption of afferent pathways of the carotid sinus caused extrasystoles which disappeared after cutting of adrenergic fibres which descend from the posterior hypothalamus (Miller)

In a certain proportion of experiments ectopic arrhythmias were observed after injection of 0 1–0 5γ of acetylcholine into the lateral ventricles (Dikshit 1934a) Such irregularities could also be produced in cats by the intraventricular injection of caffeine and nicotine sodium barbitone given intracerebrally or intravenously lessened or abolished such arrhythmias provoked by caffeine (Dikshit 1934b) Dikshit concluded that caffeine can produce cardiac irregularities by some action on the hypothalamic centres

In unanaesthetized dogs intracerebral (ventricular) injection of strophanthin produced numerous extrasystoles followed by ventricular tachycardia of about three hundred per minute Such arrhythmias were abolished by intravenous barbital but not by vagotomy This effect was specific for strophanthin the only other substance which was found to have a somewhat similar though considerably less marked effect was pitressin Histamine caused auricular but never ventricular extrasystoles (Korth Marx and Weinberg)

Allen (1931b) obtained in rabbits similar results regarding chemical or faradic stimulation of the hypothalamus in three animals premature systolic arrhythmias followed such stimulation (In the few instances in which arrhythmias were produced by strong faradic stimulation of the superior colliculi this was attributed to the concomitant marked rise in blood pressure as no such arrhythmias occurred if the rise in blood pressure was kept below 5 mm Hg) On the other hand the arrhythmias produced by insufflation of benzol persisted after section of the brain in a plane similar to that which Brow and his collaborators found in cats to abolish chloroform extrasystoles Allen concluded that the pathway is through some connexion between the trigeminal and a centre below the diencephalon

A similar mechanism seems to have been present in the arrhythmias produced in dogs by intracisternal injection of potassium phosphate (a m/6 mixture of mono and di potassium phosphate of p_H 7 6) (Walker Smolik and Gilson) The irregularities consisted in ventricular extrasystoles at times occurring as bigeminal rhythm They were abolished by section of the cord at the level of the sixth cervical vertebra though they could still be elicited by tetanic stimulation of the spinal cord just below the level of section or by stimulation of one or the other stellate ganglia especially the left They were not abolished by brain stem transection in the intercollicular or pontile region and were more pronounced after vagotomy With intact vagi ectopic beats occurred more frequently during inspiration when the heart rate was higher and in the case of bigemini the coupling of the extrasystoles was constant even if respiratory arrhythmia was marked It is considered possible that the arrhythmias were due to stimulation of cells in the floor of the fourth ventricle causing excitation of pathways which descend in the spinal cord and leave in the sympathetic nerves at the upper thoracic levels Ectopic impulse formation was enhanced by the absence of vagal influence and was independent of the hypothalamus

Regarding ventricular tachycardia produced by adrenaline in dogs under cyclopropane anaesthesia it was found that no such arrhythmia occurred in two dogs after a lesion in the pons at the level of the trigeminal nerve (Allen Stutzman and Meek)

As far as the efferent pathways are concerned the stimulation of which produced and the section of which prevented or abolished ectopic arrhythmias due to chloroform benzol or cyclopropane the paramount importance of the sympathetic that is the *rami communicantes* of the upper thoracic segments and the stellate ganglia has been established by the work on these subjects discussed in this chapter The above findings that stimulation of the posterior and lateral parts of the hypothalamus produces such arrhythmias accords well with these observations since it is known that these parts of the hypothalamus contain

centres of vital importance for the activity of the sympathetic nervous system Contrariwise vagal stimulation tends to prevent or abolish ectopic arrhythmias in such circumstances It may be mentioned that stimulation of the tuber nuclei of the hypothalamus which are known to be concerned with the function of the para sympathetic produced slowing of the heart and lengthening of the A V conduction time from 0 06 to 0 08 second (Beattie 1932 a b) but no ectopic arrhythmias were observed

That the importance of the sympathetic nervous system as efferent paths in ectopic arrhythmias of central nervous origin is not confined to those of hypothalamic origin is shown by the part it plays in the extrasystolic irregularities produced by the intracisternal *injection of potassium phosphate di cussed above*

Also abnormal electro encephalograms were reported during the occurrence of neurogenic arrhythmias (Weinberg 1947) and attacks of paroxysmal tachycardia were observed in infants with encephalitis (Bernuth and Steinen)

In electroshock ectopic arrhythmias were found in a considerable proportion of the electrocardiograms recorded in 304 major convulsions in 126 consecutive curarized patients (atrial 26 per cent ventricular 18 7 and nodal 5 9) their incidence was much higher in seventy tracings taken from patients with cardiovascular disease the corresponding figures being 47 1 40 0 and 7 1 per cent respectively (Hejtmancik *et al*) In a series of ten patients treated with electroshock eight showed arrhythmias of which auricular extrasystoles were the most frequent (Altschule *et al*)

In exceptional circumstances however stimulation of the vagus may produce extrasystoles in the experimental animal (*see* p 255) Regarding a possible central vagal origin of extrasystoles in man a clinical observation of Korth may be quoted in a digitalized patient of fifty eight with auricular fibrillation and an old standing mitral lesion numerous ventricular extrasystoles occurred after an apoplectic fit due to embolism in the basilar artery and resulting in a softening of the left cerebellar hemisphere The extrasystoles which were abolished by atropine were considered central in origin and due to an involvement of the vagal nucleus If the explanation is correct the observation would demonstrate in man a central vagal origin of extrasystoles in the presence of digitalis as a sensitizing agent This would be analogous to the experimental production of extrasystolic arrhythmias by peripheral vagal stimulation in dogs sensitized with aconitine or to the extrasystoles elicited by stimulation of the central end of the vagus in chloroformed cats (Korth) The alternative explanation that the extrasystoles were due to impairment of vagal action by the cerebral lesion is unlikely in view of their abolition by atropine

The question of a central nervous origin of extrasystoles may be of medico legal importance as shown by the first of two cases reported by Lucke A man of fifty four sustained concussion by a fall from a ladder, and a cardiac arrhythmia discovered after the accident was at first thought to indicate previous heart disease which was considered to have caused *the accident Subsequent fuller investigations failed to reveal any evidence of a cardiac* lesion prior to the accident and it was concluded that the accident was the cause of the arrhythmia This consisted in blocked auricular extrasystoles the disturbance of conduction being abolished by 1 mg of atropine The arrhythmia was still present one year after the accident though its character had somewhat changed (Lucke) In our opinion unless there is proof to the contrary in a case of this kind an arrhythmia may well have been present unnoticed for quite a time before the accident and may have caused the fall

Regarding the part played by the central nervous system in the production of ectopic arrhythmias it is clear that here again complex conditions are present whenever such cardiac irregularities are observed (For a short summary *see* Weinberg 1948) Certain parts of the brain stand out as of particular importance in this connexion such as the hypothalamus pons and the floor of the fourth ventricle but different parts play the leading role according to the conditions of the experiment According to these the afferent paths through which

the impulses precipitating the arrhythmias travel also vary widely Regarding the efferent paths the predominant importance of the sympathetic became manifest at almost every stage of the discussion but a few conditions have been shown to exist in which surprisingly the vagus enhances or precipitates ectopic impulse formation and the roles usually played by vagus and sympathetic seem reversed

The relationship between extrasystoles and emotional factors is discussed in the chapter dealing with predominantly clinical aspects of such arrhythmias (*see* p 448)

SUMMARY

In this chapter the influence of the nervous system in eliciting or modifying ectopic arrhythmias is discussed Using the term nervous system to include the action of auto nomic nerves reflexes the central nervous system and psychological factors this influence is profound and of great physiological and clinical importance

It is pointed out that in most cases in which nervous influence precipitated or modified ectopic and allied arrhythmias complex conditions were present which resulted in the heart s being predisposed to the exhibition of such disturbances of rhythm

The influence of the nervous system in this respect is discussed in some detail under the following headings

Ectopic beats precipitated by direct (faradic) stimulation of vagus and sympathetic
- due to reflexes
  - from the carotid sinus including the part played by the presso receptor nerves
  - from the respiratory tract
  - from the gastro intestinal tract
- precipitated from the central nervous system

The relevant literature about these aspects is reviewed and several personal observations are described

Regarding the relationship between emotional factors and ectopic arrhythmias the reader is referred to the appropriate section of the chapter on Some mainly Clinical Aspects of such arrhythmias (p 448)

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CHAPTER VIII

EXTRASYSTOLES DRUGS AND ELECTROLYTES

INTRODUCTORY REMARKS

There is hardly a chemical compound which is not known to have precipitated extra systoles in certain circumstances It would be as unprofitable as it is impossible to give a complete list of such substances and to attempt anything like a review of the literature on this topic Instead an endeavour has been made to select in this chapter certain com pounds which are of a special physiological or clinical interest regarding their relation to extrasystoles or ectopic arrhythmias generally and to confine discussion to the more important aspects Moreover it is hoped that the various bibliographies will be found helpful by those who are especially interested in any particular aspect

As combination of drugs has often to be discussed some repetition is not entirely avoidable but by making use of cross references we have tried to reduce it as much as possible Much work is in progress at the moment on some of the drugs discussed for example on procaine and related compounds so that many of the most recent papers could not be included and any conclusions on such compounds should be considered as neces sarily provisional

DIGITALIS

Of all the innumerable drugs which have some relation to ectopic arrhythmias digitalis unquestionably occupies pride of place It shows *par excellence* the dual property of being able to elicit as well as to suppress such disturbances of rhythm With a drug employed on such a vast scale its modes of action are bound to assume the greatest im portance physiological as well as clinical

Experimental

Introductory Remarks

While a review of the complex mode of action of digitalis would be out of place in this book a few remarks are opportune about its effect on the refractory phase and on cardiac excitability these aspects having a close bearing on the subject under discussion

In this connexion it hould be recalled that in addition to its direct effect on cardiac muscle digitalis exerts an indirect one through increasing vagal tone In the mammalian heart the latter is confined to auricles and the A V node since direct vagal influence does not extend to the ventricles

In the auricles increase of vagal tone results in a pronounced shortening of the refractory period Regarding the direct effect upon the heart muscle of the drug in this respect it was formerly believed that this consisted in a l ngthening of the period of refractoriness (Lewis Drury Wedd and Iliescu) In view of the method employed in such experiments (discussed in the section on quinine) such results were subsequently queried by Lewis and collaborators themselves re investigation of this problem with an improved technique revealed that digitalis invariably shortened the absolute refractory period in the ventricle of the tortoise (Love) and of the dog (Lewis and Drury) These conclusions were in accord ance with those of Junkmann and subsequently were repeatedly confirmed (Schellong

McLeod Wedd Blair and Dwyer) The pronounced shortening of the Q T intervals in the electrocardiograms of man during digitalis treatment also indicates a shortening of the refractory period (Berliner) Certain reservations seem however to be necessary Lewis and Drury when reversing their original views pointed out that what they termed the effective refractory period (that is the interval required for a subsequent stimulus to yield a *propagated* wave of excitation) is lengthened by strophanthin and Schellong arrived at similar conclusions

That digitalis diminishes the excitability of the heart has been known for a long time (Traube 1871 Tschistowitsch Brandenburg Hering 1907, Sollmann *et al* Guthrie) It seems desirable to recall such observations as the contrary statement can be found in some textbooks namely that digitalis increases cardiac excitability Such statements are based on the assumption erroneous in our opinion that the precipitation by digitalis of ectopic beats indicates increased excitability of the heart Such reasoning seems to us open to doubt since increased excitability alone does not give rise to ectopic impulses

Experimental Investigations on Ectopic Arrhythmias Caused by Digitalis and Strophanthin

Amongst the earliest observers of arrhythmias caused experimentally by digitalis Traube (1850–51) may be mentioned and particularly Boehm who reported in 1872 that in frogs the diastolic part of the wave was interrupted half way by the rudiment of a second systole (our translation) and found similar conditions in dogs His explanation—that digitalis increases the contractility to such an extent that two contractions became necessary to exhaust it—seems a little naive to day though eighty years intensive research have still not exhausted the problem Other early reports include those of Popper (1889) François Franck (1894) and Cushny (1897)

The first systematically to investigate electrocardiographically the arrhythmias occurring in dogs as a result of strophanthin and digitalis were Rothberger and Winterberg in 1913 In all stages of strophanthin intoxication ectopic beats were found originating as a rule in the left ventricle During the early stages of the drug effect such ectopic beats occurred only if the normal impulse formation in the S A node was inhibited by faradic stimulation of the vagus During higher degrees of intoxication they were observed without vagal stimulation and with still more pronounced poisoning ventricular ectopic rhythms completely replaced sinus rhythm These results were confirmed by Egmond and by Scherf (1927b)

The dose of strophanthin or digitalis necessary to elicit such ectopic arrhythmias varied as reported by different investigators In an early study on dogs Halsey found 19–33 per cent of the m l d of strophanthin necessary for precipitating terminal ectopic arrhythmias (precursors of ventricular fibrillation) whereas at least 40 per cent were required if digitalis was employed Later investigations gave almost the same figure regarding strophanthin (18 per cent Hoekstra and Schleusing) whereas those for digitalis varied between 20–30 per cent in dogs (Seevers and Meek) and 50 per cent (Levine and Cunningham) and 63 per cent in cats (Bauer and Reindell) If ephedrine was given in conjunction with digitalis such arrhythmias were more pronounced and persistent and ventricular fibrillation occurred at an early stage (Johnson and Gilbert Seevers and Meek)

One important feature of such ectopic arrhythmias caused by digitalis or strophanthin is that bigeminal rhythms due to extrasystoles with constant shape and constant coupling in the electrocardiogram were never observed The irregularities of rhythm consisted of ectopic ventricular beats occurring singly with varying coupling or in groups with varying shapes and in irregular sequence Even if the drugs were administered in high doses which usually cause complete A V block true extrasystoles with the above mentioned characteristics so common in clinical experience could not be elicited experimentally (Tabora Egmond) As distinct from extrasystoles in the strict sense of the term such experimental

digitalis or strophanthin arrhythmias have to be considered as due to increased auto maticity of ventricular centres The importance of this distinction is discussed in the chapter on Mechanism

In view of the paramount clinical importance of bigeminal rhythms due to extrasystoles attempts were made experimentally to produce this type of arrhythmia by modifications in technique

One such approach was to combine the administration of the drugs with other measures Intensive damage to the myocardium by administration of phosphorus prior to the injec tion of digitalis was unsuccessful mechanical damage of the bundle branches undertaken concurrently with the injection of strophanthin had only a very limited success (Kobacker and Scherf) The only method known to us by which it was possible to produce by the systemic administration of strophanthin extrasystolic arrhythmias with extrasystoles of constant shape and accurate coupling is by its combination with the inhalation of a mixture of 25 per cent CO_2 and 75 per cent O_2 (Goldenberg and Rothberger) Administration of such mixture at the stage of ectopic (pre fibrillary) tachycardia quickly converted it into a polygeminal rhythm and finally into a true bigeminy This procedure was reversible the former irregular tachycardia recurring within a few seconds on substituting air for the above gas mixture

Another method consists in the *topical* application of digitalis to the surface of the ex posed heart As early as 1894 Langendorff observed abnormal arrhythmic pulsations after the application of digitalis or helleborein to the isolated apex of the frog s heart A similar method was used when strophanthin lanatoside C or digitoxin was applied in dogs to the exposed heart *in situ* (Scherf 1944 Kisch 1944) Figs 161 and 162 illustrate arrhythmias produced in this way

Fig 161a shows persistent trigeminy recorded six minutes after the subepicardial injec tion of 0 05 cc of a 0 1 per cent solution of ouabaine into the conus of the right ventricle The first extrasystole of each trigeminus is accurately coupled to the preceding sinus beat and the interval between the two extrasystoles equals the coupling All extrasystoles have the same shape The arrhythmia persisted for six minutes

Fig 161b demonstrates ventricular extrasystoles with accurate coupling and constant shape occurring after every second sinus beat the arrhythmia was elicited by brushing a 0 1 per cent solution of digitoxin on a circumscribed area of the conus of the right ventricle Similar results were obtained by the application to the epicardial surface of a few crystals of strophanthin or digitoxin

The assumption that such extrasystoles originate in the area to which the drug had been applied is supported by the observation that warming by a thermode of this area accelerates the extrasystolic rhythm This is illustrated in Fig 162 the beginning of which shows an irregular ventricular tachycardia which had been elicited by the application of strophanthin (strophosid Sandoz) to the conus area of the right ventricle During warming of this area a conspicuous increase in rate occurred though the shape of the ectopic beats remained un changed in the record

Extrasystoles produced in this way immediately disappeared when the sinus rhythm was inhibited by vagal stimulation This demonstrates that they were precipitated by the preceding (sinus) beat and were not due to an independent automatic activity of the ectopic centre

A more detailed analysis of the extrasystolic arrhythmias produced by such methods revealed several points of interest They occurred after a considerable latent interval amounting in the case of strophanthin to about six and in that of digitalis to about eleven minutes A similar latent period was seen with the topical application of barium but not with that of sodium (Piccione and Scherf *see* respective sections) Such arrhythmias lasted for a considerable time that is up to twenty two minutes in the case of strophanthin

FIG 161 —From experiments on dogs *a* Lead 2 Persistent trigeminy after the subepicardial injection of 0 05 cc of a 0 1 per cent solution of ouabaine into the conus of the right ventricle *b* Ventricular extrasystoles with accurate coupling and constant shape after every second sinus beat after topical application of a 0 1 per cent solution of digitoxin to the conus of *the right ventricle*

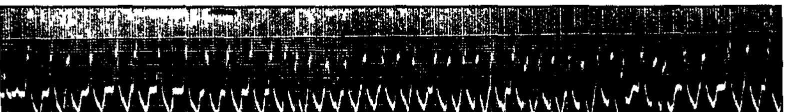


FIG 162 —From an experiment on a dog The beginning of the tracing shows an irregular ventricular tachycardia elicited by the topical application of strophanthin to the conus area of the right ventricle Warming of this area (between the two marks on the record) resulted in an increase in rate of the ectopic rhythm

and up to forty five minutes in that of digitalis Extrasystoles could be elicited from any part of the auricles or ventricles which was tested by this method If as was occasionally observed ventricular tachycardias occurred they showed the same kind of irregular sequence as those precipitated by the focal application of barium or by the systemic administration of digitalis or strophanthin in larger doses

These observations emphasize an essential similarity between the arrhythmias caused by the topical application of strophanthin (or digitalis) and barium as distinct from sodium and warrant the conclusion that they are a specific drug effect and not due to local mechanical or osmotic stimulation Furthermore such extrasystoles have to be assumed to originate in one circumscribed focus in which they are precipitated by the preceding beat they occur without the automatic impulse formation in other ventricular centres being altered Hence also as distinct from the arrhythmias due to systemic administration of strophanthin or digitalis the constant shape and accurate coupling of the ectopic beats (and the possibility of eliciting them from auricular centres) The significance of these views in relation to our conception of the mechanism of extrasystolic impulse formation and also to its separation from automatic impulse formation is discussed in the chapter on Mechanism

In studies on isolated strands of Purkinje tissue of dogs hearts digitalis or strophanthin caused arrhythmias akin to bigeminal or trigeminal contractions (Wachstein Spuehler and Zwillinger Ferranini)

Auricular ectopic arrhythmias caused by systemic administration of digitalis were reported by Cushny (1897)

Arrhythmias caused by injection of strophanthin into the fourth ventricle are discussed in the chapter on Nervous System (p 268)

Clinical Observations

The occurrence of arrhythmias in the course of digitalis treatment has been known for a long time Mention must be made in this context of Traube s description of the irregular pulse (1850-51) similar observations were made by Lorain in 1870 and by Riegel in 1877 (*see* also Josue and Godlewski 1912 and chapters on Historical Remarks and on Coupling) In particular the bigeminal pulse was bound to attract attention at an early stage

It was soon recognized that different patients varied widely regarding the dose of digitalis necessary to produce irregular pulse and heart action

Predisposing Factors of Ectopic Digitalis Arrhythmias

It is a curious fact that in normal subjects digitalis does not cause ectopic arrhythmias *This was recognized by Huchard as long ago as 1892 and later obs rvations have shown that* even lethal doses taken accidentally or with the intention to commit suicide do not precipitate extrasystoles though abnormal rhythms and A V block were found (Eckstein Froment *et al* Tomaszeski and Lapa McGuire and Richards Duvoir *et al* Albeux Fernet and Welti Bickel *et al*) unless structural heart disease is present (Wilkinson) While the statements that extrasystoles occur only in patients with hypertrophy or dilatation of the heart (Edens) or with increased serum calcium (Edens and Huber) were not confirmed there is a great deal of evidence that ectopic digitalis arrhythmias are observed only in patients with some structural heart disease This is already implicit in Huchard s writings of 1892 (*cp also* Fauconnet 1904) MacKenzie (1905) emphasized the frequency with which digitalis causes bigeminal rhythm in patients with rheumatic valvular disease and with auricular fibrillation The opinion expressed repeatedly (Huchard Gallavardin 1926a) that digitalis extrasystoles are especially common in patients with enlarged hearts due to

rheumatic mitral valvular disease and that they carried an unfavourable prognosis (Huchard Leconte Edens and Huber Gallavardin 1926a) was confirmed by Scherf (1932) who found that amongst twenty one consecutive patients with digitalis bigeminy twelve had mitral lesions and that sixteen of this series died within eighteen months aft r the arrhythmia had been discovered These figures are comparable with those of Edens and Huber who reported a mortality of 80 per cent within two years While such extrasystoles are very common in auricular fibrillation they are by no means rare in sinus rhythm We agree with Leconte s description that digitalis extrasystoles are a geste de souffrance rather than with minimizing the prognostic significance of this kind of arrhythmia (Gold and Otto)

If structural heart disease is a predisposing factor for digitalis extrasystoles it is not the only one This follows from the great individual differences regarding the dose required to produce them While some patients with unquestionably diseased hearts can take large doses of digitalis over long periods without exhibiting any extrasystoles though pronounced disturbances of conduction testify to the marked drug effect others develop bigeminal heart action after very mall doses For example in one observation 0 1 gramme of powdered *(assayed) leaves taken three times for one day only caused extrasystoles which disappeared* within a few days of discontinuing the drug to re appear whenever the above small dose was re instituted (Scherf 1932) Not infrequently extrasystoles or bigeminy are seen in a digital ized patient soon after a mercurial diuretic had been given this is due to a re digitalization of the patient by re absorption and re circulation in the body of fluids with a high content of digitalis The other extreme is represented by patients who develop extrasystoles only after several years treatment with large doses of digitalis In one patient observed for many years a woman with hypertension grossly enlarged heart and auricular fibrillation a weekly maintenance dose of 5 5 mgm of digoxin was taken for years with hardly any extrasystoles on periodical electrocardiographic examinations (Schott unpublished observation)

The rate at which the premature beats disappear after discontinuation of the drug equally varies within very wide limits ranging from a very few days to one month it is known that it may take that time for the drug to be eliminated from heart muscle

What the cardiac condition is which predisposes the heart to such arrhythmias the nature of this terrain cardiaque special (Gallavardin 1926a) is not known

Descriptive Features of Digitalis Extrasystoles

Extrasystoles caused by digitalis have two important characteristics with rare excep tions they are ventricular in origin and their shape in the electrocardiogram is not constant whereas their coupling practically is

Auricular Ectopic Digitalis Arrhythmias It should be emphasized that the great majority *of digitalis extrasystoles originate in the ventricles While the cause of this is not known* it is likely that vagal tone which is increased by the drug and which in the mammalian heart does not affect the ventricles is of importance in this connexion The statement that such extrasystoles may originate in auricles or ventricles and are only more common in the latter (Cushny *et al* 1912 Luten Katz) seems in this general form to give a misleading idea about the frequency of auricular extrasystoles which are only rarely caused by this drug

One such instance was reported by Heyl in which auricular extrasystoles and auricular tachycardia occurred whenever digitalis was given The possibility that paroxysmal auricular tachycardia (or flutter or fibrillation) may occasionally be caused by this drug has been pointed out by Decherd Herrmann and Schwab and by Stone A personal obser vation may be added

Fig 163 reproduces records from an eighty six year old woman with arteriosclerosis and moderate dilatation of the heart blood pressure 180/90 Digitalis was prescribed by her medical adviser because of moderate dyspnoea 0 8 mgm of digitaline Nativelle being

given as an initial dose followed by a daily maintenance dose of 0 4 mgm On the fifth day of this treatment the patient exhibited profound general muscular weakness nausea and yellow vision an electrocardiogram taken at that time is shown in Fig 163a It demonstrates auricular tachycardia with an auricular rate of 186 inverted P waves in leads 1 and



Fig 163*a*
Auricular tachycardia and multiform ventricular extrasystoles due to digitalis

2 and multiform ventricular extrasystoles The RS T segments and T waves show a marked digitalis effect The drug was discontinued immediately and ten days later another electrocardiogram (Fig 163b) showed sinus rhythm without extrasystoles in the final deflections some digitalis effect is still present though far less pronounced

Ventricular Ectopic Digitalis Arrhythmias Whereas some authors are of the opinion that digitalis extrasystoles are constant in shape and thus do not differ from the common variety occurring spontaneously (for example Lewis) we believe that generally their shape

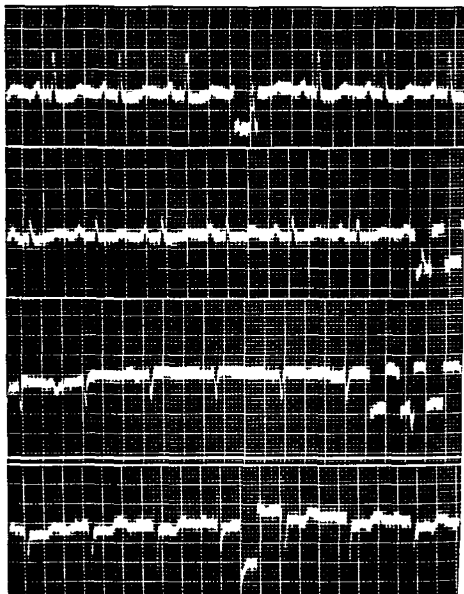


FIG 163*b*

From the same patient as Fig 163*a* Ten days after discontinuing digitalis Sinus rhythm For further explanation see text

varies in the electrocardiogram a view held also by others (for example Gallavardin 1926a Mahaim) In a series of fifty eight consecutive cases with extrasystoles due to digitalis such changes in shape of the extrasystoles were encountered in every case (Scherf 1931 1932)

Often the form alters from extrasystole to extrasystole It is true that in some cases longer tracings have to be taken in order to detect greater variations in shape and short records may reveal only differences in the height or depth of the several waves in such instances differences in the appearances of the extrasystoles tend to become more pronounced as digitalis treatment continues (Scherf 1927a) In other cases however conspicuous variations in shape of the extrasystoles are seen from the very beginning of the arrhythmia and longer records have to be available to discover even two premature beats having exactly the same configuration For these reasons digitalis extrasystoles have sometimes been called multifocal but such designation seems to us of questionable accuracy since disturbances of conduction of the extrasystoles originating in one focus cannot be excluded as the underlying mechanism and actually seems the more likely alternative in some instances This view is supported by the observation that in spite of their varying in shape digitalis extrasystoles have a fairly constant coupling in eleven out of fifteen cases variations in coupling did not exceed 0 02 second (*see also* chapter on Coupling) Multiform seems to be a better term

As stated elsewhere multiform extrasystoles indicate structural heart disease In view of what has been said above regarding digitalis extrasystoles this statement can be amplified by adding irrespective of whether they are observed without digitalis or are precipitated by this drug

In cases in which digitalis causes ectopic arrhythmias extrasystoles occur at first singly but bigeminal heart action soon becomes established This has been described on numerous occasions amongst the early papers may be mentioned those of Mackenzie 1905 Lewis 1910 Robinson and Bredek Clarke *see also* Sagall and Wolff

If at this stage the exhibition of the drug is continued further developments take place along one of three lines

(1) Bigeminy persists (2) the extrasystoles disappear (3) the extrasystoles increase in number and with further continuation of digitalis treatment ventricular tachycardia and lastly ventricular fibrillation ensue Each of these possibilities warrants a more detailed discussion

(1) Persistence of bigeminy in the course of continuation of digitalis treatment in full doses is comparatively rare In such cases the number of extrasystoles does not increase nor do automatic idioventricular beats occur In one personal observation a patient with coronary sclerosis and two attacks of myocardial infarction 0 2 g of powdered leaves daily had to be given for two and a half years in spite of the continuous presence of bigeminy Whenever the drug was stopped the patient s condition deteriorated rapidly This type of response is observed in about 10 per cent of cases (Scherf 1932)

(2) In other instances amounting to about 30 per cent the extrasystoles disappear during the continued exhibition of digitalis and do not re appear even if the drug is administered in undiminished doses for a long time In some of these patients on the other hand some reduction in the dose is necessary to make continuation of digitalis treatment without increase in the number of premature beats possible

(3) The largest and clinically the most important group reacts to the continued administration of digitalis by an increase in the number of extrasystoles The bigeminy changes into tri or polygeminy and eventually in ventricular tachycardia and ventricular fibrillation Several electrocardiographic aspects merit special consideration

One variety seen in more advanced digitalis intoxication is the occurrence of automatic idioventricular beats to which extrasystoles may be coupled in a similar way as to supraventricular beats Fig 164 provides an example it was obtained in a patient with auricular fibrillation in the course of digitalis treatment continued through many months Extrasystoles of varying shapes can be seen throughout the record The sixth and seventh

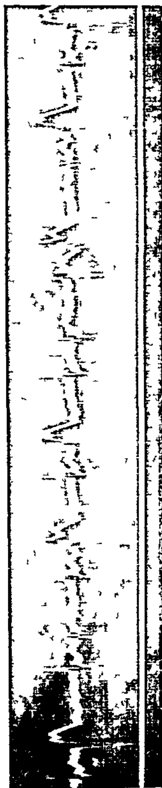


FIG 164.—From a patient with auricular fibrillation Automatic idioventricular beats and extrasystoles due to digitalis For further explanation see text

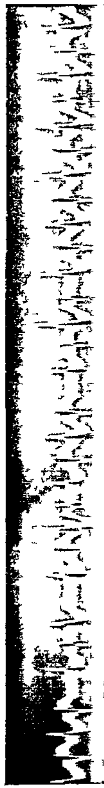


FIG 165.—Lead I Polygeminy and ventricular tachycardia with alternating shape of complexes due to digitalis For further explanation see text

extrasystoles follow an automatic idioventricular beat with the same coupling as those coupled to supraventricular beats Such idioventricular beats should not be confused with extrasystoles They are recognized as such by their occurrence late in diastole They also may show continual variations in form (Christian 1915b)

Sometimes automatic and extrasystolic beats have the same form in the record which indicates origin in the same focus (compare the great similarity between the second extra systole and the second automatic beat [the thirteenth complex] in Fig 164) similar observations have been made by Rachmilewitz and Scherf and by Scherf and Schott (*see also* chapters on Pararrhythmia and on Mechanism)

Other varieties are polygeminy and ventricular tachycardias with alternating shape of the ectopic beats Fig 165 illustrates both The tracing was obtained from a patient with emphysema shortly after the injection of 0 2 mgm of strophanthin It shows auricular fibrillation The first supraventricular beat is followed by two the second by seven ventricular extrasystoles all having different shapes The third conducted beat is followed by a ventricular tachycardia with alternating shape of the complexes In some cases such alternation is maintained for considerable periods In order to explain the alternation various views were put forward

(a) A rather complicated circus movement was assumed involving the two ventricles alternately (Gallavardin 1926a Palmer and White) As there are no data pointing to the existence of such paths in the ventricles this hypothesis for which no proof was attempted can be disregarded

(b) The presence of two centres of impulse formation alternating in action was postulated by Felberbaum It has to be remembered however that not infrequently such tachycardias are entirely regular and that no alternation of cycle length is associated with alternation of form It would be difficult to imagine an exactly equal rate of impulse formation in two centres situated in different ventricles This hypothesis has to be considered improbable though not impossible

(c) The most probable explanation seems to be the assumption of impulse formation in one centre with alternation of intraventricular conduction (Scherf and Kisch) This view is supported by experimental and clinical observations regarding similar alternation of ventricular complexes in instances of auricular tachycardia in which such alternating intraventricular conduction is observed in respect of supra ventricular beats An example is provided in Fig 137 in the chapter on Coupling

Such tachycardias are often precursors of ventricular fibrillation and therefore have an ominous significance (tachycardie terminale Gallavardin 1926b) In elderly patients they may be observed after moderate doses of digitalis (Currens *et al*) They call for immediate discontinuation of the drug Occasionally this arrhythmia is encountered without digitalis (four out of eighteen cases Scherf and Kisch *see also* Fig 198) In one such case the tachycardia was observed in an otherwise healthy subject for many years and could always be stopped by digitalis (Scherf and Kisch) Ventricular tachycardia even with alternating shape of the complexes if not caused by digitalis is no contra indication against giving this drug (Scherf and Kisch *see also* Gilson and Schemm)

It is easily understood that arrhythmias of this type have repeatedly been reported at a time when rapid digitalization (for example Eggleston s method of administering within twenty four hours large doses of the drug calculated by the patient s weight) was practised on a wider scale (Schwensen Felberbaum Reid 1923 1924 Marvin Palmer and White) Owing to the present revival in the U S A of this way of digitalis administration such arrhythmias are being described again with increasing frequency (Levine Stone Fremont and King)

While ventricular tachycardia and particularly its variety with alternating complexes

if caused by digitalis is an absolute contra indication against continuing medication con ditions are more complicated if bigeminal rhythm or single extrasystoles occur during digitalis treatment According to Mackenzie digitalis bigeminy is a signal to lessen at once the dose no good is obtained by pushing it further Christian (1915b) stated that it is a sign of omission of digitalis Leconte s view was that it is permissible to continue the treatment if single extrasystoles occur but that it is necessary to stop the drug immediately the number of extrasystoles increases

Our views may be summed up thus If extrasystoles had not been present before the *exhibition of digitalis and occur in the course of its employment* great care on the physi cian s part is always called for to continue with the drug always requires special precautions and if at all practicable repeated electrocardiograms Furthermore each case must be con sidered individually and we would discourage all generalizations With these provisos we recommend that having regard to the arrhythmia the drug be discontinued if the maximum beneficial effect on congestive heart failure had been attained which can be expected in the individual case in other words if compensation had been restored as fully as is reasonable to expect In nearly all such cases a smaller maintenance dose has to be re instituted which can usually be effected after a short interval of say 2–3 days The situation is different in cases in which extrasystoles occur at a stage of treatment when congestive heart failure is still pronounced and when with further exhibition of the drug further improvement can be expected In such cases continuation of the drug in temporarily reduced doses under strict supervision and repeated electrocardiographic control is justified This view is based on the fact discussed above that for the development of such arrhythmias in the course of digitalis treatment the condition of the heart in the individual case is of as much impor tance as the dose of the drug and that in a certain proportion continuation of medication does not increase the number of the premature beats Should the arrhythmia become more pronounced immediate cessation of the drug treatment is imperative

Similar problems sometimes arise in the treatment of certain arrhythmias In one such instance a patient with Lutembacher s syndrome and auricular flutter with occasional ventricular extrasystoles bigeminal heart action developed in the course of digoxin treat ment the cautious continuation of drug treatment made the desired conversion into auricular fibrillation possible (Schott)

It will have become evident that success or failure will in many cases depend on the optimum adjustment of the dose of the drug in the individual case and much has to be left to the physician s discretion and experience This is not possible with the administration of large amounts of the drug within a short time (*see* above) For the same reason we advise to employ the same principle when using intravenous injections of strophanthin we recom mend that the first dose should not exceed 0 15 mgm and the patient be closely observed for the occurrence of premature beats for thirty minutes Only in the absence of extra systoles should the daily dose be increased to 0 25 mgm and the strict supervision of the patient should be continued after each injection 0 5 mgm should never be exceeded and this dose seems rarely necessary Strophanthin should not be given if the patient had taken *digitalis within ten days before the intended injection With these precautions* the use of strophanthin can be considered safe (Laubry and Leconte Simici)

The Abolition of Extrasystoles by Digitalis

Extrasystoles which are not due to digitalis usually disappear when this drug is given This therapeutic effect upon extrasystoles of digitalis is discussed in the section on Treat ment There are very few statistical data on this type of its action In one investigation digitalis was found to cause a marked reduction or disappearance of extrasystoles in six out of eight cases In the two remaining instances the patients developed terminal ventricular extrasystoles shortly before death (Otto and Gold)

Other Glucosides with Digitalis like Action

Regarding extrasystolic arrhythmias too such glucosides have an action similar to digitalis Experimentally bigeminal action was observed after the administration of apocynum cannabium (Hecht) and squills (Turnbull) The effect of scillaren upon isolated strands of *Purkinje tissue was similar to that of digitalis or strophanthin described above (Rothberger and Zwillinger)* The administration of water insoluble glucosides of squills caused extrasystoles in twelve out of twenty five cases (Maher and Sittler) Similar effects were seen with foliandrin (Schindel and Braun) and with helleborein both experimentally (Hering 1901) and in clinical observations (Scherf 1937) In all such instances the ectopic beats were ventricular in origin and showed continual variations in shape

SUMMARY

Experimental Investigations

Some work on the effect of digitalis on the refractory period and on the excitability of the heart is briefly discussed Systemic administration of strophanthin or digitalis results in ectopic arrhythmias originating in a ventricle whereby the ectopic beats have varying shape and varying coupling in the electrocardiogram Extrasystoles in the strict sense of the term (that is with accurate coupling and often of constant shape) so common in clinical practice cannot experimentally be produced by the systemic administration of these drugs except by the concomitant inhalation of a mixture containing 25 per cent CO_2 and 75 per cent O True extrasystolic arrhythmias can on the other hand be elicited by the topical application of these drugs to the surface of the exposed heart *in situ* Such arrhythmias are discussed in some detail and the importance of such investigations for the experimental reproduction of a common clinical disturbance of rhythm is emphasized The significance of such investigations is pointed out regarding our views about extrasystolic as distinct from automatic impulse formation and about the mechanism of the origin of extrasystoles discussed in more detail in the appropriate chapter

Clinical Observations

It is pointed out that digitalis or strophanthin does not cause extrasystoles in normal subjects and that some predisposing factors are necessary for such arrhythmias to be precipitated by these drugs Structural heart disease is one such factor some aspects of which are discussed in detail The dose of the drug necessary to elicit extrasystoles varies widely in different cases and so does the time required for them to disappear after cessation of medication Of the features of digitalis extrasystoles the comparative rarity of auricular ones is stressed and one personal observation of such an instance is described The varying shape but fairly constant coupling of ventricular digitalis extrasystoles are emphasized as important characteristics The development of extrasystolic arrhythmias during digitalis treatment is discussed under the three headings (1) persistence of bigeminy (2) disappearance of extrasystoles during continued digitalis treatment (3) increase in the number of extrasystoles resulting in tri or polygeminy ventricular tachycardia and ventricular fibrillation The occurrence of automatic idioventricular beats is mentioned as one variety of such arrhythmias The association of automatic idioventricular beats with extrasystoles is discussed and illustrated by a personal observation Ventricular tachycardias with alternation of the complexes are described in some detail illustrated by one personal observation and the various explanations of this arrhythmia are critically discussed The dangers as exemplified by such arrhythmias of the administration within a short time of large doses of digitalis are strongly emphasized and recommendations are given as to the continuation or otherwise of the exhibition of digitalis in cases in which extrasystoles occur or increase in numbers in the course of its exhibition The adoption of similar principles

in the employment of strophanthin given intravenously is briefly discussed Some work on the effect of other glucosides with a digitalis like action is briefly reviewed

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QUININE AND QUINIDINE

Some Introductory and Historical Remarks

Though Senac wrote in 1749

> De tous les remedes stomachiques celui dont les effets m ont paru les plus constants & les plus promts en beaucoup de cas c est le *quinquina* mele avec un peu de rhubarbe Des palpitations rebelles & longues ont cede à ce febrifuge seconde d un leger purgatif

the value of quinine was not generally known until it was rediscovered by a patient of Wencke bach (1914) who realized the great importance of this observation Wenckebach retold the story in 1923 It is true that long before 1914 individual observers amongst them eminent clinicians recommended quinine often with other measures for the treatment of patients with irregular heart action some of whom may well have had extrasystolic arrhythmias (Oppolzer 1866 Sir Walter Foster 1890 Hochhaus 1907 Huchard 1908) and it must have been as early as 1892 that Wm Pepper (of the University of Pennsylvania) recommended cinchona and bromides to Walsh who suffered from extrasystoles for decades (Walsh 1927)

In 1918 quinidine another alkaloid of the cinchona bark and an isomer of quinine was

found by Frey to be more effective than quinine in the treatment of cardiac arrhythmias and is now universally used for this purpose The note about quinidine in the epitome of the U S *Pharmacopea and National Formulary of* 1916 at one time recommended as a cheap substitute for quinine Inferior and obsolete (White Marvin and Burwell) thus became obsolete

Frey s observations about the superiority of quinidine over quinine were repeatedly confirmed (Lewis Drury Wedd and Iliescu Drury Horsfall and Munly Clerc and Deschamps Boyer) Lewis *et al* (1922) found quinidine about five to ten times more effective than quinine According to Weisman (1942) commercial quinidine contains 80 per cent of pure quinidine which is a marked cardio vascular depressant and 20 per cent of hydro quinidine which has only slight depressant properties

While at present quinidine sulphate is almost exclusively used in the treatment of cardiac arrhythmias it should be remembered that in this respect qualitatively quinine has the same effect as quinidine

Experimental Findings

The quinine alkaloids are general cell and protoplasmatic poisons Their most important effects upon the heart can—somewhat artificially—be summarized thus

(1) Effect on excitability
(2) Effect on impulse formation
(3) Effect on refractory period
(4) Effect on vagus
(5) Effect on conductivity

While some particulars of the above modes of action as far as they are relevant in the context of this book will be briefly discussed under these headings it should be emphasized that the various properties are interdependent and that it is thus hardly ever possible fully to analyse the resulting effect in a given set of circumstances

(1) Fffect on Excitability

A depressant effect upon excitability of quinine alkaloids has been demonstrated in various ways (Hofmann 1915 Hirschfelder and Cervenka) The threshold for eliciting ectopic beats by electrical stimuli was found to be raised by quinine alkaloids (Hofmann 1915 Drury *et al* Lewis *et al* 1921 Wedd Blair and Gosselin Wegria and Nickerson) The chronaxie of the myocardium is increased (Espanes) In experiments on cats and dogs treated with quinine even prolonged faradic stimulation of the ventricles did not elicit persistent fibrillation (Hecht and Rothberger Boekelman) In the perfused surviving heart of man quinine was found to diminish contractility stimulus formation and excitability (*Boden and Neukirch*)

(2) Effect on Impulse Formation

Like so many compounds cinchona alkaloids may suppress as well as precipitate ectopic beats The first of these predominates

Depression of ectopic impulse formation was observed by Santesson *in 1893 in the* isolated heart of the frog spontaneous irregularities of rhythm disappeared when quinine was added His observation has repeatedly been confirmed Various investigators reported that ectopic beats caused by digitalis were abolished by quinidine (Pezzi and Clerc Jackson *et al* Clerc and Deschamps Haskell Friedberg and Levinson) Those produced by strophanthin responded in the same way Suppression of ectopic arrhythmias elicited in dogs by means of barium were stated by Singer and Winterberg to be abolished by quinine but this

(3) Effect on Refractory Period

In considering the effect upon the refractory period of quinidine it has to be noted that its direct effect may be modified by its paralysing action on the vagus and by its effect on excitability

That quinidine lengthens the refractory period as it had first been reported by Santesson in 1893 seemed established by repeated subsequent confirmations (Drury Horsfall and Munly Lewis Drury Iliescu and Wedd de Boer Junkmann and Starkenstein Decherd and Ruskin) Such work was based on the determination of the time interval at which cardiac muscle responded to an early testing shock applied after a conditioning shock It was then found that the response or non response of the heart to a test shock applied in such circumstances was not a reliable criterion for determining the refractory period as non response may be due not to absence of excitability but to extinction of the impulse by disturbances of conduction If this source of error was eliminated shortening by quinidine of the absolute refractory period was found in the ventricle of the tortoise (Love) and of the dog (Lewis and Drury) This does not however affect what Lewis and Drury termed the *effective* refractory period namely the interval required for a subsequent stimulus to yield a propagated wave of excitation this effective refractory period is lengthened by quinidine Experiments on isolated strands of Purkinje tissue did not yield uniform results (Berk and Wachstein)

(4) Effect on Vagus

There is general agreement that quinidine paralyses the vagus to a greater or less extent This vagal action increases the direct effect of quinidine upon the auricles as it tends to prolong the refractory period and to slow conduction Differences of opinion exist as to the site of the drug effect but a discussion of the various views is outside the scope of this book (*see* Dale Clerc *et al* 1922 Lewis *et al* 1922 Hiatt *et al*) Recently a sympathicolytic effect of quinine and quinidine has also been described In dogs quinidine counteracts the pressor effect of epinephrine and of the stimulation of the splanchnic nerve (Hiatt 1950)

(5) Effect on Conductivity

This may be summed up by quoting Lewis (1925 p 359) In fact the general statement may be made that the alkaloid quinidine depressed conduction in all the muscular tissue of the heart

Clinical Observations

As stated in the introductory remarks to this section appreciation of the value of quinine in the treatment of extrasystoles is due to Wenckebach (1914) and of the superiority of quinidine to Frey (1918) Their reports about the beneficial effects of these



FIG 166 —From an experiment on a dog The beginning of the record shows bigeminal rhythm resulting from faradic vagal stimulation during the action of aconitine Quinidine transformed this arrhythmia into ventricular tachycardia shown in the second part of the record From SCHERF and SIEDEK *Z ges exp Med*

alkaloids were soon confirmed (Smith 1922 Deschamps Levine and Fulton Gouley and Soloff) Some dissenting opinions (for example Lian and Blondel) while understandable in view of the occasional refractory case can be disregarded

It was stated by Singer and Winterberg that quinidine suppresses ventricular extrasystoles more readily than auricular ones

The detailed mode of action by which quinidine abolishes extrasystoles in man cannot be stated with any degree of certainty The result is likely to be due to a combination of several factors namely the effect of the quinine alkaloids on excitability stimulus formation and perhaps also on conductivity and refractory period

Experimental and Clinical Observations on Absorption and Elimination

In connexion with the practical application of these compounds data concerning their rate of absorption and elimination are important some relevant papers may be briefly discussed

Lewis *et al* (1922) studied the effect of specially purified cinchona alkaloids in patients with auricular fibrillation After one single dose of 0 8 gramme of quinidine an effect was first noticeable after thirty minutes and was fully developed after one and a half and three and a half hours It had subsided after twenty four to thirty hours save in exceptional cases when some residual effect could still be traced after forty hours

The results obtained by Weisman (1940) in dogs are in agreement with the findings of Lewis and collaborators Weisman found that after a single *small* oral dose of 100 mgm the maximum concentration in the heart muscle was reached in about thirty minutes and no trace was present at the end of four hours When repeated doses of 100 mgm each were given three or four times at one hourly intervals the maximum concentration in the myocardium was seen after two hours After a single *large* dose of 585 mgm the maximum concentration in the heart muscle was observed in about one hour and it took seven hours before the last trace had disappeared from the heart If approximately the same large dose of 585 mgm was given in three divided doses at one hourly intervals (200 mgm three times) the maximum concentration in the heart was reached only after two hours and attained only 50 per cent of that produced by giving the same amount as a single dose Similar results were obtained by others (Weiss and Hatcher) Comparable time relations were found in man by Sigall Horn and Riseman who used the changes in the Q T interval as criterion to measure speed and duration of the effect of this group of drugs

This difference regarding the maximum concentration of quinidine in the heart and the speed at which it is reached is important for the mode of clinical application of this drug it has often been observed that for the purpose of stopping auricular fibrillation or paroxysmal tachycardia the exhibition of quinidine in a few large doses is superior to that of the same total quantity in more frequent smaller single doses

Linenthal *et al* (1947) found that in man after one single dose of 0 2–0 6 gramme of quinidine the alkaloid could be traced in the plasma after fifteen minutes maximum concentrations were found after one to three hours and maintained for two to three hours appreciable amounts could still be traced after eight to twelve hours According to Linenthal and Freedberg following an oral dose of 0 2 gramme of quinidine the peak level of the drug in the plasma was 0 8 mgm per litre while it was 2 7 mgm per litre when a single oral dose of 1 0 gramme had been given There was always a clear correlation between plasma levels and therapeutic effects In some patients arrhythmias disappear with plasma levels of 2 and 10 mgm per litre Sokolow and Edgar found significant quantities of quinidine in the blood even twelve to twenty four hours after the administration of one single oral dose the average residual level after twelve to eighteen hours was 42 per cent of the peak level Such observations that this alkaloid can be traced in the blood many hours after the exhibition of one single dose conflict with the experimental results of Weisman and of

Weiss and Hatcher discussed above They are of interest in view of the generally accepted view that the pharmacological effect is clinically limited to a few hours and that the drug is quickly eliminated Personal experience shows however that the effect of one oral dose lasts longer than some of the experimental work would lead one to expect

A comparative study of the plasma levels reached with the same total daily dose of about 1 gramme by different members of this group of drugs showed considerable differences the plasma concentrations of cinchonine were generally less than 5 per cent of those of quinine and those of quinidine (and cinchonidine) were intermediate between these two extremes (Taggart *et al*)

Quinidine is partly destroyed in the liver (Plehn) and partly eliminated by the kidneys According to Taggart *et al* less than 5 per cent is excreted by the kidneys Renal excretion is relatively smaller with the exhibition of one large dose than with the administration of the same amount in divided doses For this reason Wiechmann recommended to give the largest possible doses in as few fractions as possible

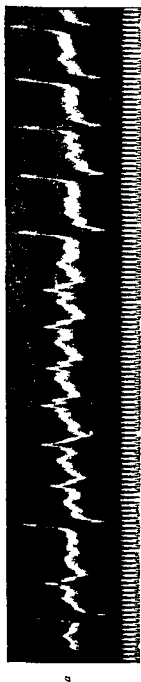
After *intravenous* administration these alkaloids disappear quickly Weiss and Hatcher found in a cat that after one single injection of 59 mgm of quinidine 95 per cent had disappeared from the blood within five minutes and after one hour only 1 per cent could still be traced Similarly seven minutes after one single injection of 10 grains of quinidine Weisman (1940) found only 6 per cent in the blood

Ectopic Arrhythmias Caused in Man by Quinidine

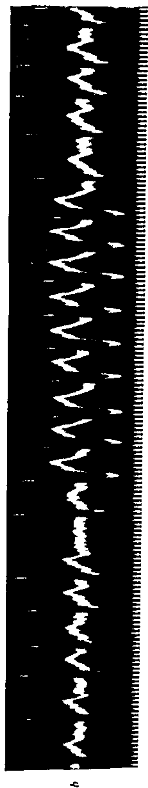
In accordance with experimental investigations clinical observations have shown that sometimes quinidine may precipitate ectopic beats or increase the number of those previously present

The majority of such observations were made in cases of auricular fibrillation in which in the course of quinidine treatment beats with abnormal ventricular complexes were recorded (White Marvin and Burwell Lewis Drury Wedd and Iliescu Levy Maynard) Such beats occur sometimes in groups of three or four in succession at other times in greater numbers presenting as short periods of paroxysmal tachycardia Lewis *et al* found such abnormal complexes in 25–30 per cent of their observations and since they were absent before and subsided soon after the discontinuation of the alkaloid they were unquestionably caused by it They tended to occur particularly at a time when quinidine had slowed the auricular rate and showed constant shape in the electrocardiogram but varying coupling Differences of opinion existed however whether such beats actually were ectopic in origin while Lewis *et al* (1922) and Wetherbee *et al* considered them to be extrasystoles White Marvin and Burwell and Gouaux and Ashman interpreted them as supraventricular beats with aberrant intraventricular conduction Wilson Wishart Clark and Herrmann who found the number of such beats increasing if quinidine was continued after the first appearance of isolated beats of this kind thought they were supraventricular in origin and attributed their aberrant intraventricular conduction to an increase in auricular rate due to vagal paralysis In one single case on the other hand Wilson and Wishart recorded such beats for two to three minutes after intravenous injection of quinidine and considered them to be extrasystoles

We have made similar observations in two cases of auricular fibrillation during quinidine treatment (Fig 167) The patient in whom Fig 167a was obtained developed the abnormal beats on the third day of treatment after a total dose of 2 grammes (after a test dose of 0 25 gramme this amount had been taken three times the first and four times the second day) In the second instance the abnormal beats reproduced in Fig 167b occurred after one week of quinidine treatment during the last two days of which the daily dose had been 2 grammes The sequence of the abnormal beats is less irregular than that of the supraventricular complexes which is suggestive but by no means conclusive of a ventricular



a



b

Fig 167 —Arrhythmias observed during quinidine treatment From two different patients For explanation see text

ectopic origin of the abnormal beats While in such cases it is not possible to decide with any degree of certainty whether such beats are ventricular ectopic ones or supraventricular in origin with aberrant intraventricular conduction complexes which we have observed after the intravenous injection of quinidine in cases of paroxysmal auricular tachycardia can definitely be considered to be extrasystoles as a confusion with aberrantly conducted sinus beats is hardly possible

Several clinical instances have been reported in which short paroxysms of ventricular tachycardia and even ventricular fibrillation were observed following the oral (Davis and Sprague Kerr and Bender) or intravenous (Schwartz and Jezer Jezer and Schwartz) administration of quinidine In most of these cases complete A V block was usually also present its relation to the abnormal response to quinidine is obscure In two cases short paroxysms of ventricular fibrillation were invariably observed on several occasions after each intravenous injection of quinidine so that a coincidence can be excluded In the case of Diamondstone *et al* the paroxysmal ventricular tachycardia cannot with certainty be attributed to the large dose of quinine which had been taken (and which also had caused amaurosis) since the patient may have had a concurrent myocardial infarction

For particulars about the therapeutic use of quinidine *see* section on Treatment

SUMMARY

Experimental Findings The various effects upon the heart of quinine and quinidine as far as they are relevant to the subject of this book are briefly reviewed namely their effect on excitability impulse formation refractory period vagus and conductivity It is pointed out that while a depressing effect upon ectopic beats of these alkaloids predominates in common with many other compounds they may also have the reverse effect that is precipitating ectopic arrhythmias

Clinical Observations are in agreement with experimental findings The importance of the quick rate of absorption and elimination of quinidine for its mode of application in clinical medicine is emphasized some relevant data are reviewed Two personal observations are described which demonstrate the precipitation by quinidine of beats with abnormal complexes occurring in groups the differential diagnosis of which is discussed The literature on ectopic arrhythmias caused by quinidine is briefly reviewed

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ATABRINE

A certain number of compounds though chemically unrelated to quinine exert upon the heart a quinine like action They include papaverine trasentin some local anaesthetics and antihistaminics syntropan and atabrine (Dawes)

Atabrine a synthetic anti malarial drug of this kind inhibits ectopic impulse formation in the heart Other quinine like actions include its antagonistic effect to epinephrine on blood pressure (Storm Melville) It also abolished auricular fibrillation in the dog (Gertler and Karp) Toxic effects consist of anorexia respiratory disturbances yellow discolor ation of the skin pain in the epigastrium and also extrasystoles (Motta Storm Smith and Stoeckle) Different species seem to vary in their susceptibility to the drug

According to Shannon *et al* atabrine di hydrochloride can in man be given intraven ously in doses not exceeding 0 4 gramme without untoward effects provided it is injected slowly but this is not recommended as a routine measure

Clinically atabrine has been successfully employed in the treatment of auricular fibril lation and paroxysmal tachycardia (Ganguli Gertler and Yohalem Vega Diaz)

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FAGARINE

Fagarine an alkaloid obtained from the Argentinian plant *fagaro cocco* has been known since 1932 to be a cardiac depressant (Stuckert and Sartori) Subsequently Espanes established that it raises the fibrillation threshold for faradic stimulation and reduces the incidence of ventricular fibrillation after ligation of coronary arteries

The therapeutic possibilities of this drug attracted greater interest during the Second World War when quinidine was scarce and alpha fagarine hydrochloride was recom mended for the treatment of cases of auricular flutter and fibrillation (Deulofeu *et al* Taquini) In one case reported by Taquini (1945) multifocal ventricular extrasystoles were observed after the administration of the drug which can only be given intramuscularly Subsequently Scherf Silver and Weinberg gave fagarine to thirteen patients with auricular flutter or fibrillation or paroxysmal tachycardia six of these developed multifocal ventri cular extrasystoles and in two instances ventricular fibrillation ensued Only two of the patients with multifocal extrasystoles had premature beats before the drug was adminis tered

In view of these observations fagarine has to be considered too dangerous to be employed in man

It should however be emphasized that in the dog even intravenous injection of relatively large doses does not precipitate extrasystoles while instantly abolishing auricular flutter and fibrillation without causing either a fall in blood pressure or dilatation of the heart (Scherf 1948) Such observations encourage the hope that some modification of fagarine may result in a drug which though effective is free from the above dangerous side effects The recent investigations of DiPalma and Lambert according to which the presence of a methoxy group is essential for the effect upon arrhythmias of quinidine fagarine and other compounds may point the way in which the search for such a remedy might be undertaken

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CHLOROFORM

While chloroform is now rarely used as an anaesthetic the arrhythmias caused by this compound are of great historical—apart from the physiological and clinical—interest For it is due to the study of the chloroform arrhythmias that the importance of ectopic beats and ventricular fibrillation was first appreciated and the close relationship between these two arrhythmias realized

Experimental

In experiments on animals under chloroform anaesthesia arrhythmias were observed at an early time (Knoll 1876) but the recording methods available at that time were inadequate for any detailed analysis The arrhythmias seen in one experiment by Oliver and Schafer (1895) as a result of an injection of adrenaline given during chloroform anaesthesia probably was one of the first reported instances of ventricular fibrillation in this condition In retrospect the bigeminal and trigeminal heart action observed in 1900 by McWilliam when the chloroform concentration in the inspired air was kept between 0 5 and 1 5 per cent can be assumed to have been due to ectopic beats

The problem was clarified by the extensive investigations of A G Levy carried out in collaboration with Lewis Chloroform administered to cats in concentrations of less than 0 5 per cent affected the heart but slightly (Levy and Lewis) only minor disturbances of cardiac rhythm were observed and ectopic beats were rare Inhalation of chloroform in concentrations between 0 5 and 1 per cent on the other hand caused ectopic beats invariably such arrhythmias usually disappeared if the concentration of the gas was further increased to above 1 5 per cent and did so invariably with concentrations above 2 per cent

The injection of 0 065 mgm of epinephrine during the inhalation of lower concentrations of chloroform caused ventricular fibrillation whereas with higher concentrations of chloro form the same dose of epinephrine precipitated only isolated ectopic beats Struggling of the animal or stimulation of the accelerans fibres had the same effect as epinephrine (Levy 1912) It could be demonstrated that the arrhythmias resulting from the combination epinephrine chloroform were not due to a rise in blood pressure and that they could be *abolished by severing the vagi (Levy 1913) this effect of vagotomy was attributed to the* tachycardia with the resultant shortening of diastole (Nobel and Rothberger) Ventricular fibrillation caused by nicotine during light chloroform anaesthesia was shown not to be a vagal effect (Levy 1926)

Levy became convinced that sudden death during chloroform anaesthesia was due to ventricular fibrillation From his extensive investigations he concluded that it is during *light* chloroform anaesthesia that the heart is in the condition of greatest irritability during which any stimulation of the adreno sympathetic system may cause death due to ventricular fibrillation (1913) During *deeper* anaesthesia with chloroform on the other hand cardiac function is only depressed but no arrhythmias occur Such depression of function by chloroform was also found in isolated Purkinje fibres of the dog s heart (Ishihara and Pick)

Levy s findings were repeatedly confirmed (Cluzet and Tixier Bardier and Stillmunkes Tiemann Beattie Brow and Long 1930 1936 Trimble) Other investigators however obtained different results Such apparent contradictions are largely attributable to differ ences in the species of animals used in the drugs employed for pre medication and in the dosage of chloroform (Embley Caine and Reynolds Meek Liebenow and Orth) The difference in the reactions of different species becomes apparent from the observations of Embley who found ventricular fibrillation during inhalation of chloroform in three out of five experiments on cats but was unable to reproduce in dogs the results which Levy had obtained in cats Fibrillation was never observed Smirnow on the other hand reported ventricular fibrillation resulting from the combination chloroform epinephrine in dogs but not in cats In a recent comprehensive review of the action of chloroform (Waters) only one instance of ventricular tachycardia was found in over three hundred inductions with chloroform on 120 dogs Deliberate maladministration (overdosage) caused marked depression of sinus node activity and abnormal automatic beats Intravenous injection of epinephrine (0 01 mgm per kilo) during chloroform anaesthesia (eighty two injections) produced ventricular tachycardia twenty one times and ventricular fibrillation seven times Pre medication with atropine (0 5 mgm per kilo) did not prevent epinephrine chloroform tachycardia but DHE 45 (0 4 mgm per kilo) afforded protection

Frommel s investigations (1927 1928) emphasize even more strikingly the importance of the species employed in such experiments working on guinea pigs he found that ectopic beats occurring during chloroform anaesthesia were not influenced by the injection of epin ephrine and he went as far as to recommend epinephrine as treatment for accidents occurring during chloroform anaesthesia This may be mentioned as a rather glaring example of an indiscriminate application to a clinical problem of results obtained in experimental work

Quinine and quinidine prevent ectopic arrhythmias caused by chloroform and by chloroform + epinephrine (Bardier and Stillmunkes 1926) Similarly decerebration of cats at the Sherrington level abolished ectopic beats produced by chloroform and if per formed prior to the administration of the anaesthetic prevents such arrhythmias (Beattie Brow and Long 1930 1936) This is discussed in some detail on pp 267–268 In dogs antihistaminics (pyribenzamine antistine) in relatively large doses inhibited ventricular fibrillation induced by chloroform and adrenaline but such effect was inconstant and only of short duration (Levitan and Scott) Regarding the effect of atropine *see* section on Atropine

Clinical Observations

Employing the electrocardiogram in a series of six patients Cluzet and Tixier found ectopic beats during chloroform anaesthesia in two instances Hill inve tigated this prob lem electrocardiographically in seventeen cases in sixteen of these special attention was paid to the induction period In seven instances numerous ectopic beats were recorded closely resembling the arrhythmias seen in experimental work Sometimes they occurred only when the patient was struggling an observation fully in accordance with those of Levy discussed above

Waters in the monograph already referred to tabulated the various arrhythmias recorded in fifty two patients during chloroform anaesthesia (Table X on p 71) These included thirty six instances of ventricular extrasystoles and twenty (!) of ventricular tachy cardia in only seven no irregularities were found These observations emphasize the risks inherent in this anaesthetic and seem to give little if any support to the contention con tained in that monograph that much undeserved blame was being placed on an agent which for almost a century has been used extensively and skilfully by practitioners

SUMMARY

The extensive investigations of Levy demonstrated that in cats light chloroform anaes thesia is apt to precipitate ectopic beats and ventricular fibrillation that epinephrine during light chloroform anaesthesia increases the tendency to such arrhythmias considerably and that sudden death occurring in such circumstances is due to ventricular fibrillation A review of the literature reveals many conflicting reports and it could be shown that such discrepancies are largely due to differences in experimental technique The different reac tion of various species is of particular importance It can be considered established that ectopic arrhythmias occur in man during chloroform anaesthesia and that in man as well as in most species used in experimental work fatal ventricular fibrillation can be precipi tated during chloroform anaesthesia by the exhibition of epinephrine and allied compounds Struggling has an effect similar to that of epinephrine and great care has to be taken in this respect by the anaesthetist in the increasingly rare instances in which chloroform is used as an anaesthetic

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CYCLOPROPANE

Cyclopropane is a cyclic hydrocarbon (trimethylene) It is now widely used as a general anaesthetic as it produces unconsciousness within one or two minutes and patients are awake *within ten minutes of discontinuing the anaesthetic*

Experimental

When this compound was first investigated prior to its introduction as an anaesthetic arrhythmias resembling missed beats were observed in the blood pressure tracings (Lucas and Henderson) Such arrhythmias disappeared quickly when the concentration of the gas was reduced

As cyclopropane was used more extensively as an anaesthetic it became recognized that next to chloroform this ga is most apt to produce ectopic arrhythmias At first ectopic ventricular beats occur singly and at long intervals then more frequently subsequently their number further increases multifocal ectopic beats are observed and finally ventricular tachycardia and ventricular fibrillation may ensue

Various views have been expressed regarding the underlying mechanism At first it was thought that ectopic arrhythmias were only produced by such high concentrations of cyclopropane as result in respiratory arrest and that a reduction of this concentration abolished the irregularities immediately (Seevers *et al*) The main responsible factor was believed to be anoxia in the presence of which ectopic beats were said to be precipitated even by low concentrations of cyclopropane such arrhythmias were reported to resemble those seen in anoxia (Robbins and Baxter 1937 Robbins 1940) With adequate respiration and ample supply of oxygen on the other hand concentrations of cyclopropane of 30 per cent above those producing respiratory paralysis were stated not to cause ectopic arrhythmias

This view that anoxia plays a decisive role in the production of cyclopropane arrhythmias was not confirmed (Lee *et al*) and if the effect of anoxia on the cardiac action generally is recalled seems questionable Generalized anoxia while producing marked disturbances of conduction of various kinds does not as a rule cause ectopic arrhythmias on the contrary certain varieties of these for example extrasystoles due to aconitine are abolished

by anoxia (Scherf) It is only local anoxia that is ischaemia of circumscribed areas as in myocardial infarction or coronary stenosis that it is apt to cause ectopic beats (*see* p 420)

Another view was that only light anaesthesia with cyclopropane causes ectopic irregularities whereas deeper anaesthesia abolishes them (Guedel) but the existence of such an arrhythmia range was denied by others (Lee *et al*) Similarly the statement that concentrations of cyclopropane between 50 and 70 per cent depress the hypothalamic centres responsible for ectopic arrhythmias (Thienes Greeley and Guedel) and thus abolish them was not confirmed (Rait Smith and Ostlere) A reflex origin of cyclopropane arrhythmias has also been assumed by several investigators (Seevers *et al* Thienes *et al*) This view was based on the observation that atropine abolished the irregularities This argument seems to us unconvincing for the ensuing tachycardia with the resulting shortening of diastole alone may suppress ectopic beats and atropine in larger doses is known to have a direct effect upon the heart muscle where it inhibits impulse formation Experiments carried out with a different technique and interpreted as indicating a reflex origin of such arrhythmias were reported by Stutzman *et al* The only conditions in which we believe a reflex mechanism to have been responsible for ectopic arrhythmias observed in man under cyclopropane anaesthesia are those described by Reid and Brace (see chapter on Nervous System p 264)

All this tends to show that there is no agreement as yet about the mode of origin of ectopic arrhythmias occurring during cyclopropane anaesthesia The only point which can be considered established is that the anaesthesia should be lightened as soon as arrhythmias occur (Eversole Sise and Woodbridge)

Other Drugs and Cyclopropane

Epinephrine enhances the formation of ectopic beats during cyclopropane anaesthesia (Meek Hathaway and Orth) similar to its effect during chloroform anaesthesia In dogs the intravenous injection of epinephrine in doses of 0 01 mgm per kg during cyclopropane anaesthesia caused ventricular tachycardia in eleven out of seventeen animals whereas in seventeen control experiments epinephrine alone precipitated such arrhythmias only once (Meek 1941) The rise of blood pressure is not the only mechanism responsible for the cardiac arrhythmias following cyclopropane and epinephrine (Moe *et al*) since compression of the aorta in dogs under cyclopropane anaesthesia does not cause arrhythmias (Murphy *et al* 1949)

Ectopic arrhythmias caused by the combination of cyclopropane epinephrine are prevented by dibenamine (Moe *et al* Nickerson and Goodman) a similar preventive effect has been claimed for morphine (Robbins and Baxter) and for barbiturates (Robbins Baxter and Fitzhugh Robbins 1940) but such effect of drugs of the latter group was questioned by others (Orth *et al* Meek 1941 Lee *et al*) Ectopic arrhythmias due to cyclopropane in dogs could be prevented by a prior injection of sodium amytal or pentothal sodium (Betlach) In a series of sixteen experiments on dogs prepared with nembutal no ectopic arrhythmias were observed during subsequent cyclopropane anaesthesia not even with concentrations of the gas up to 75 per cent (Scherf unpublished observation)

Other compounds stated to prevent such arrhythmias in dogs are yohimbine ergotamine and procaine (Allen *et al* Bennett Dhuner and Orth) Inhalation of ether has been recommended with discontinuation of cyclopropane as soon as arrhythmias appear After the tissues have been saturated with ether it is claimed that renewed use of cyclopropane does not elicit arrhythmias (Milovsky and Rovenstine cf also Johnstone)

The effect of procaine in such arrhythmias is discussed in the section on Cocaine and Allied Compounds (p 309)

Clinical Observations

On the whole these are in agreement with experimental findings Isolated ectopic beats occurring at first singly then in increasing numbers and ventricular tachycardia with multiform ectopic beats have been reported in man during cyclopropane anaesthesia (Kurtz Bennett and Shapiro) This development closely resembles that during chloroform anaesthesia *A high degree of protection by the intravenous administration of barbiturates has* been reported amounting in the case of pentothal to 90 per cent (Guedel) The value of full doses of atropine in pre medication for the prevention of arrhythmias during cyclopropane anaesthesia has recently been stressed by Rink Helliwell and Hutton (*see* section on Atropine) Regarding the suppression of such arrhythmias by ether *see* below, also section on Ether (p 309)

Johnstone studied the heart rhythm electrocardiographically in ninety patients anaesthetized with cyclopropane with special reference to the presence or otherwise of hypoxia CO_2 accumulation and hyperventilation He found that it was the accumulation of CO_2 which precipitated ventricular arrhythmias Hypoxia did not appear to have any influence on such arrhythmias They could be abolished by ether For their effective control the effective elimination of CO and avoidance of respiratory depression is recommended

Freeman saw ectopic ventricular beats occasionally during manipulation of the vagus in patients under cyclopropane anaesthesia

While the occurrence of ectopic arrhythmias during cyclopropane anaesthesia can be considered established they do not occur invariably Waters found such arrhythmias in 2 22 per cent of cases with the patient in Plane I and in 12 72 per cent with the patient in Plane IV In a series of forty one cases studied by Kurtz *et al* such arrhythmias were observed in 10 per cent Ziegler found extrasystoles and paroxysmal tachycardia in 10 per cent of 175 children with congenital heart disease and cyanosis submitted to the Blalock Taussig operation under cyclopropane anaesthesia These arrhythmias subsided under ether and oxygen

The conditions favouring the occurrence of such cardiac irregularities are still obscure An admixture of other hydrocarbons has been considered Cyclopropane is widely used to the great satisfaction of anaesthetist and surgeon In cardiac patients this type of anaesthesia is avoided by many and ether preferred Alimurung and Smith attribute the absence of serious cardiac arrhythmias in their series of ten patients submitted to operation for coarctation to the fact that cyclopropane was not used Moreover cardiac dilatation was observed to be caused by this compound (Brace *et al*) There is general agreement that in combination with cyclopropane the use of epinephrine and of allied compounds (pressor amines) is dangerous

SUMMARY

In man and in dogs cyclopropane causes ectopic arrhythmias in a considerable proportion of cases In spite of extensive experimental work some of which is briefly discussed the mechanism responsible for such cardiac irregularities is still obscure The use of epinephrine in cyclopropane anaesthesia is dangerous Drugs having a preventive effect are discussed Of these procaine amide seems to be the most promising (*see* section on Cocaine and Allied Compounds)

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OTHER HYDROCARBONS

Propylene which is an isomer of cyclopropane has been investigated in experiments on cats and dogs (Caine and Reynolds) Ectopic beats originating in various foci in the ventricles were observed they disappeared when the concentration of the gas was reduced No extrasystoles were observed in nine experiments performed on one individual in whom this anaesthetic was used (Kahn and Riggs)

Trilene (trichlorethylene) belongs to the chlorinated hydrocarbons and in this respect is related to chloroform Though less toxic than carbon tetrachloride it is apt to cause ectopic arrhythmias (Geiger) Hewer (1941 1943) studied fifteen cases during anaesthesia electrocardiographically and found auricular extrasystoles in one and ventricular ones in

two instances He emphasized the frequent occurrence of auricular extrasystoles (Hewer 1943) Frequent extrasystoles were also observed by others (Gordon and Shackleton Hunter) but reports about the relative incidence of auricular and ventricular extrasystoles are conflicting In an electrocardiographic study on forty patients (thirty males ten females) Barnes and Ives found a great variety of arrhythmias The incidence in per cent of those due to ectopic beats was auricular extrasystoles 12 5 ventricular 40 coupled beats 27 5 multifocal ventricular contractions 15 multifocal ventricular tachycardia 10 These authors found that as a rule ectopic arrhythmias occurred later—during the lower first or upper second plane—than other arrhythmias though exceptions were observed They point out that arrhythmias giving the clinical impression of being due to auricular fibrillation were probably cases of multifocal ventricular tachycardia This observation makes special care in the use of this anaesthetic imperative

Isopropyl chloride (Proponesin) was found to produce pronounced arrhythmias including multifocal ventricular extrasystoles in healthy subjects and caused fatal cardiac arrest in a patient with thyrotoxicosis (Elam and Newhouse)

The effect of various hydrocarbons combined with epinephrine was studied by Chenoweth who investigated in particular benzene heptane gasoline (65 octane) butane and hexane All these compounds were found capable of sensitizing the mammalian heart for epinephrine to induce ventricular fibrillation The practical implication of these observations is that apparently trivial accidents quarrels and other disconcerting episodes may render an individual highly susceptible for some minutes to ventricular fibrillation if to the discharge of epinephrine is added exposure to the various substances described Aeroplanes and armoured vehicles in which a combination of emotional stress and petrol fumes normally exist are places *par excellence* where such accidents may occur by this mechanism In a later study Garb and Chenoweth investigated the comparative effect of the hydrocarbons chloroform and benzene and the non hydrocarbons ether alcohol and acetone on the irritability of heart muscle (isolated papillary muscle preparation) and found that the former produced a marked increase in irritability whereas the latter were far less active In a further series of experiments on cats these authors studied the relation of drugs affecting the sympathetic nervous system to the initiation of ventricular fibrillation It was found that during hydrocarbon inhalation (petroleum ether) epinephrine and *nor* epinephrine produced ventricular fibrillation whereas N isopropyl epinephrine a purely inhibitory compound failed to have this effect though producing other arrhythmias Dibenamine (3 mgm per kg) while not altering the vasopressor effect of 10 or 30 micrograms per kilogram of epinephrine exerted a protective effect

Ectopic arrhythmias due to the inhalation of benzol were found by Nahum and Hoff in cats and monkeys during induction or during recovery that is with low concentrations Beta methyl choline prevented such arrhythmias whereas quinine failed to do so The authors claim that the ectopic beats were of multifocal origin is not borne out by the reproduced electrocardiograms

Ventricular extrasystoles were seen in one human case of acute benzol poisoning (Rossmann)

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ETHER

As compared with chloroform and cyclopropane ether causes ectopic arrhythmias only rarely This is true for experimental work as well as for clinical observations Regarding the former in many hundreds of experiments we never observed ectopic arrhythmias in dogs anaesthetized with ether (with or without pre medication with morphia) and can confirm similar earlier observations of Cluzet and Tixier and of Caine and Reynolds Not even when pressor amines were given did ectopic beats occur (Meek Orth *et al*)

Some exceptions were reported for instance in guinea pigs (Frommel) and in highly trained dogs (Betlach)

In man too ectopic arrhythmias during deep ether anaesthesia are rare or absent (Cluzet and Tixier Hill)

Whenever extrasystoles were observed they were of the supraventricular type (Meek) Kurtz Bennett and Shapiro found auricular extrasystoles four times amongst twenty patients anaesthetized with ether

The suppression by ether of ventricular arrhythmias during cyclopropane anaesthesia has repeatedly been observed (Milovsky and Rovenstine Johnstone *see* section on Cyclopropane Rink Helliwell and Hutton whose paper is more fully discussed in the section on Atropine Stein and Buchberg)

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COCAINE AND ALLIED COMPOUNDS

Experimental Investigation

The earlier observations that cocaine preparations applied to the epicardial surface may diminish the excitability of the heart as tested by mechanical or electrical stimuli and thus prevent the occurrence of extrasystoles (François Franck 1892 Heitler 1898 Froehlich 1904 Kochmann and Daels 1908 Fauconnier 1908 Froehlich and Paschkis 1923) did not

attract much attention at the time but became of increasing interest as thoracic surgery developed With the rise of cardiac surgery the importance of such compounds was further enhanced since manipulation of the heart is apt to cause extrasystoles in operations for congenital heart disease or adhesions of the pericardium (Feil and Rossman Stewart and Bailey, Ziegler)

Mautz (1936) confirmed the earlier work that after the local application of cocaine or meticaine on the epicardial surface of the heart the threshold for the production of extra systoles by means of induction shocks was increased and Beck and Mautz recommended the intrapericardial injection of 2 cc of a 5 per cent solution of procaine or meticaine in order to reduce the risk of extrasystoles during operations on the heart

Cocaine and related substances if applied directly to the cardiac surface cause im mediate depolarization (Baron)

The intravenous administration of this group of compounds is the method most fre quently employed at the present time for preventing extrasystolic arrhythmias during anaesthesia It has been demonstrated in experiments on dogs anaesthetized with chloro form or cyclopropane that ventricular fibrillation resulting from the injection of epin ephrine could be prevented by procaine or a similar compound for example p amino benzoic acid (Hermann and Jourdan Van Dongen Shen and Simon Burstein *et al* 1940)

Ventricular fibrillation produced in dogs by the administration of benzol in combin ation with adrenaline could also be prevented by the simultaneous injection of 8 10 mgm per kg of novocaine (Shen) Even in the stage of ventricular tachycardia was procaine found effective in preventing ventricular fibrillation (Burstein *et al* 1940) Reports about the action of intracardiac injection of this drug once ventricular fibrillation had become established are conflicting while Burstein *et al* (1940) found that it restored sinus rhythm in 66 per cent of the dogs Stutzman *et al* reported even large doses without effect In the dog s heart Wiggers and Wegria observed that the threshold for the production of ventri cular fibrillation by faradization was increased According to Hirschfelder and Tamcales procaine pantocaine and nupercaine stop in dogs auricular fibrillation produced by faradiz ation

Large doses of cocaine preparations are known to damage the heart in the dog an intravenous injection of cocaine or novocaine in a 2 5 or 5 per cent solution may cause right bundle branch block (Shookhoff) and focal application of cocaine to the sinus node produced sinus block and A V rhythm (Hofmann Rothberger and Scherf) Ventricular tachycardia was observed by Tainter Dock and Brown and multifocal ventricular ectopic beats—precursors of ventricular fibrillation—were reported by Uhley and Wilburne It has however been pointed out by Doak and Selke that either the doses employed in these experiments were extremely high or that the rate of injection was very fast If procaine is given by means of slow infusion and in smaller doses as it is employed in clinical practice the compound is quickly hydrolysed in the blood and the electrocardiographic changes are very slight

Regarding the recently introduced procaine amide see below in this section

Clinical Observations

In a small series (six) of healthy humans the intravenous administration of 1 g of procaine (0 1 per cent in physiological sodium chloride solution given in the course of one to three hours) produced in the electrocardiogram only minor changes without any clinical significance (Doak and Selke)

In fourteen patients under a general anaesthetic the intravenous administration of 30–70 mgm of procaine (in a 1 per cent solution) abolished acute arrhythmias often dramatically (Burstein 1946) No untoward effects were observed regarding respiration or

central nervous system Fraser and Kraft found a combination of pentothal and procaine effective in preventing irregularities due to cyclopropane Barbour and Tovell successfully employed a slow intravenous infusion of a weak solution of procaine as a preventive (1 000 cc of a 0 1 per cent solution infused within one hour) Bittrich and Powers used a 1 per cent solution giving it as a continuous intravenous infusion in seventeen cases In five instances extrasystolic arrhythmias occurred in spite of such infusion being given at a rate of 60–100 drops per minute and in one case it was found necessary to increase the rate of flow to 150 drops per minute In two patients procaine precipitated convulsions Schaffer Stein man and Scherf studied the effect of procaine on various arrhythmias One group of eleven patients received an intravenous drip of 300–500 mgm procaine hydrochloride given in a 0 1 per cent saline solution in the course of 8–30 minutes A second group of twenty one patients were given 100 mgm by means of a rapid intravenous injection (10 cc of a 1 per cent solution injected within about four seconds) The effect on extrasystoles (ventricular seven auricular five cases) was disappointing In three cases the drug precipitated extrasystoles In auricular flutter the decrease in auricular rate may result in an increase of the ventricular rate owing to a greater number of impulses being conducted (akin to similar observations made with quinidine) In the doses given it proved a safe though rather ineffective procedure

Recent reports on the usefulness of procaine in combating cardiac arrhythmias during thoracic surgery are more optimistic Thus Ziegler in a series of 175 children with cyanotic and twenty with acyanotic congenital heart disea e submitted to operation encountered premature contractions in twenty three and paroxysmal ventricular tachycardia in three instances and mentions procaine amongst the measures to stop multiple extrasystoles and ventricular tachycardia Burstein *et al* (1949) studied cardiac arrhythmias electrocardio graphically in thirty three cases submitted to thoracic surgery for various conditions Ec topic arrhythmias were found to be pronounced in the three instances of pericardiectomy during manipulation of the pericardium for their suppression the authors recommend the topical application of a 2 per cent solution of procaine as well as the rapid intravenous injection of 100 mgm of this drug in a 1 or 2 per cent solution Taylor *et al* using a 1 per cent solution of procaine and starting with 40 mgm per minute in adults concluded that procaine is relatively effective in preventing cardiac arrhythmias during intra thoracic operations with cyclopropane They warn against too rapid administration after starting These conclusions are based on 211 administrations mainly in thoracic operations no electrocardiograms were taken

An unusual observation has been reported by Lampson Schaeffer and Lincoln con cerning a seven year old boy operated upon for laceration of a foot The patient had pre medication with morphia and atropine also seconal anaesthesia was inducted with cyclo propane and continued with ether After the operation was finished ventricular fibrillation suddenly occurred Artificial respiration was given the chest opened and the heart was massaged after intracardiac injection of 3 cc of a 1 per cent solution of procaine followed by a second injection of 2 cc The fibrillation stopped and the boy recovered

Untoward effects and even fatal accidents have been reported as a result of novocaine and allied compounds In some instances they were due to overdosage in others to hyper sensitivity of the patient Sensitivity to this group of drugs varies considerably amongst different individuals and some can tolerate large doses in a recent paper Burstein (1949) reported instances in which doses of 1 000 mgm were inadvertently given intravenously with no worse effect than occasional twitching The combination with large doses of epinephrine is dangerous (Mayer) Even focal application of this combination may produce untoward effects in a patient a spray on the nasal mucous membrane of 20 per cent novo caine with 10 minims per ounce of adrenaline 1 1 000 resulted in bundle branch block with multifocal ventricular extrasystoles (Young and Glauber)

Notwithstanding such observations it can be said that the administration of procaine in doses of 300 mgm given slowly by intravenous infusion in the course of twenty to thirty minutes or of 100 mgm given by rapid intravenous injection within a few seconds is a safe procedure

Procaine is hydrolysed in the human body into p amino benzoic acid and diethylamino-ethanol The effect upon arrhythmias of the latter was investigated by Rosenberg *et al* and the compound found fairly effective in suppressing in man ventricular extrasystoles and tachycardias but not auricular ones It was however less effective than procaine and doses employed were 0 5–5 grammes intravenously in a 11 2 per cent aqueous solution In dogs diethylaminoethanol prevented ventricular tachycardia induced by epinephrine during cyclopropane anaesthesia (based on Meek Hathaway and Orth) and was the only compound of two homologous alcohol series tested in this respect to do so in non toxic doses (Mark Lott Cooper and Brodie)

In a search for a drug possessing the activity of procaine without its toxicity various esters of diethylaminoethanol were examined for stability and for their efficacy in preventing the epinephrine induced ventricular tachycardia in dogs under cyclopropane anaesthesia The most promising compound to date is the amide of procaine (N (2 diethylaminoethyl) p aminobenzamide) (Pronestyl) which is unaffected by the enzyme responsible for the rapid hydrolysis of procaine and which in therapeutic doses does not produce central stimulation This drug is also effective by mouth (Mark Berlin *et al*) According to a recent report (Kayden Brodie and Steele) it was tried in fifty five patients with ventricular extrasystoles and administered either orally or intravenously in doses of 0 4 to 1 0 gramme suppressed the ectopic beats for a period varying from a few minutes to many hours It proved particularly effective in controlling ventricular tachycardia which was terminated in fourteen out of sixteen patients by this drug given orally intravenously or by both routes Amongst these were eight who had myocardial infarction and seven in whom quinidine in large doses had been unsuccessful With oral administration hypotension which is observed as a sometimes serious side effect during intravenous administration did not develop and the oral route is therefore the method of choice The effective oral dose was found to vary widely in different patients An initial dose of 1 25 grammes followed in one hour by an additional 0 75 gramme if the tachycardia persisted proved adequate in the majority of cases but if necessary subsequent doses of 0 5–1 0 gramme every two hours may eliminate the arrhythmia In some cases the exhibition of the drug is necessary for a longer period in order to prevent the recurrence of extrasystoles or ventricular tachycardia the suggested maintenance doses range from 0 5 to 1 0 gramme every three to six hours In cases in which the drug has to be given intravenously it should be given slowly (100 mgm /minute or less) and blood pressure and electrocardiogram continually observed Good results with Pronestyl in the suppression of ventricular ectopic arrhythmias were also reported by Diaz and Cabrera Kinsman *et al* and Berry *et al*

A recent experimental study of Harris *et al* showed that the rate of ectopic ventricular arrhythmias elicited in dogs by his method of occluding a coronary branch (p 421) was markedly reduced by procaine amide Complete abolition of ectopic activity was seen only exceptionally but the ectopic rate became so slow that the risk of ventricular fibrillation was practically eliminated Furthermore the marked reduction in ectopic rate resulted in a great improvement in dynamic efficiency of the heart In instances of low frequency ectopic rhythms the effect of Pronestyl was variable and unpredictable (Procaine administered intravenously had either no or only a very transient suppressor effect on such ectopic rhythms)

Recently this compound has also been successfully employed for the suppression of multiples arhythmies ventriculaires precipitated by card ac catheterization (injection of 5–9 ml of a 10-per-cent solution through the catheter van den Heuvel Heymans)

While Pronestyl seems to be a definite advance in the treatment of ventricular extrasystoles and tachycardias its effect on auricular arrhythmias while not as firmly established at the moment seems to be promising (Schlachman *et al* Berry *et al*) Schaffer Blumenfeld Pitman and Dix found that an intravenous injection of 600 mgm abolished auricular extra systoles for several hours and converted auricular paroxysmal tachycardia flutter and fibril lation into sinus rhythm As already mentioned the intravenous injection has to be given very slowly the blood pressure should be closely observed during the injection which should be stopped as soon as the blood pressure falls to any marked extent Like many other drugs Pronestyl was found occasionally to precipitate extrasystoles The oral administration often produced nausea diarrhoea and headache Schaffer made a quantitative comparison between the anti arrhythmic potency of procaine amide and quinidine in cases with persistent auricular and ventricular extrasystolic arrhythmias He found that weight for weight quinidine is approximately four times as strong as procaine amide For every grain of quinidine necessary to obtain a certain therapeutic effect 0 25 gramme of Pronestyl was found necessary In his experience the intravenous injection of Pronestyl is superior to quinidine the usefulness of procaine amide given by mouth is limited by nausea and vomiting

Observations on larger numbers of cases must be awaited before the value of this most recent drug can be assessed more definitely Our provisional opinion is that procaine amide is very useful in ventricular extrasystoles and ventricular tachycardias after coronary occlusion in such cases it may be life saving since not infrequently such patients do not respond to quinidine In addition Pronestyl is helpful in instances of intolerance to quinidine which are by no means rare Its application in auricular arrhythmias seems promising

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BARBITURATES

Barbiturates even if given intravenously do not affect cardiac function in any appreciable way provided the dose is small the heart in good condition and the injection given slowly Larger doses have a depressant effect the diminished excitability causing ectopic beats to disappear

Experimental

Ectopic arrhythmias produced in a variety of ways have been reported to be abolished reduced or prevented by barbiturates A few examples may be quoted

In cats Dikshit found a great reduction by sodium barbitone in the number of ectopic beats produced by clamping of the carotid arteries or by intracerebral (ventricular) injection of caffeine (*see* also p 268) Braun and Samet observed also in cats that the intravenous injection of 0 1–0 15 gramme per kg of Luminal sodium increased the threshold for faradic currents to cause ventricular fibrillation This was confirmed for cats and dogs by van Dongen who also found that luminal abolished ectopic arrhythmias precipitated by epinephrine and by barium chloride Similarly such arrhythmias resulting from ephedrine were prevented in dogs by an injection of sod barbital given 125–200 minutes before that of ephedrine This effect was attributed to a partial vagal paralysis and to a central depressant action on automatic centres (Meek and Severs)

The action of barbiturates on arrhythmias due to cyclopropane where they were claimed by some to be an effective depressant is discussed in the section on Cyclopropane

While barbiturates do not cause arrhythmias (Gruber Hafkesbring and MacCalmont) thio barbiturates are known to have this effect if given intravenously in dogs 10 mgm may cause ventricular bigeminy (Gruber) Following an intravenous injection of sodium thio pentobarbital ectopic beats occurred after a latent period of six minutes This was confirmed in dogs cats and rabbits by Kohn and Lederer who did not however find such arrhythmias in five monkeys after the intravenous injection of pentothal

Clinical Observations

Clinical observations on the effect upon arrhythmias of barbiturates are few Dikshit studied a patient with numerous extrasystoles occurring at regular intervals within thirty minutes of being given 1 gramme of sodium barbiturate by mouth the number of extra systoles had become reduced by half this effect lasting for two hours

Regarding thio barbiturates no extrasystoles were seen in seventeen patients after the intravenous administration of such compounds (Volpitto and Marangoni) Extrasystoles are not a feature in patients anaesthetized with pentothal (which is a thio barbiturate) (Kohn and Lederer)

SUMMARY

Barbiturates tend to abolish prevent or diminish the number of ectopic beats caused in various animals by various methods this holds good particularly for the arrhythmias resulting from clamping of the carotid arteries from cyclopropane epinephrine or ephedrine Similar conditions seem to prevail in man but the number of clinical observations is inadequate for forming a definite opinion

Thio-barbiturates cause ectopic arrhythmias in certain animals but do not exert such effect in man

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SALICYLATES

Experimental

Only very few experimental observations on the incidence of extrasystoles after administration of salicylates have been reported No such arrhythmias were found in the isolated heart of the frog and turtle (Salant and Johnson) and in the heart *in situ* of rabbits (Renz)

Clinical Observations

Lommel described in 1902 extrasystoles during administration of salicylates in a patient with pyrexia and pleurisy and considered the possibility that the arrhythmia may have been due to the drug Subsequently similar observations have repeatedly been reported particularly in patients with rheumatic fever (Leconte Danielopolu Bass Marchal and H de Balsac Laubry) Leconte had the impression that extrasystoles were particularly prone to occur after prolonged salicylate treatment and considered their presence as a sign of saturation of the body with the drug

In hardly any of these investigations has any evidence been put forward that the ectopic beats actually were due to salicylates and were not caused by the underlying disease for which the patient was given salicylate treatment The position is somewhat reminiscent of that regarding A V block occurring during salicylate treatment of patients with rheumatic fever in the past this had frequently been attributed to the drug until the true situation was established namely that the disturbances of conduction were never due to the drug but a common sign of the disease

The only case which is somewhat suggestive is the isolated observation of Danielopolu on a boy of seventeen with rheumatic fever In this case extrasystoles occurred during the exhibition of salicylates disappeared when medication was discontinued to re appear when the drug was re instituted

SUMMARY

We concur with the view expressed by Parkinson *et al* that the precipitation of extrasystoles by salicylates cannot be considered established and that to say the least it is doubtful whether salicylates produce such arrhythmias

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EPINEPHRINE (ADRENALINE) EPHEDRINE AND ALLIED PRESSOR AMINES

Epinephrine is one of the most important compounds regarding the production of ectopic arrhythmias and this is true for the physiological as well as the clinical aspect The arrhythmias resulting from epinephrine in association with other drugs are of paramount importance Those occurring during chloroform and cyclopropane anaesthesia and in association with various hydrocarbons are discussed in some detail in the appropriate sections to which the reader is referred as well as to the chapter on Extrasystoles and the Nervous System

Experimental

Epinephrine

Arrhythmias occurring at the height of the action of epinephrine were noted early in experimental work but since at the time such irregularities were only recorded by means of blood pressure tracings a more detailed analysis of the types of arrhythmia is not possible

An early electrocardiographic study by Kahn (1909) showed ectopic beats in the dog following the intravenous injection of 0 1 mgm of epinephrine Subsequently Levy pointed out that in these experiments chloroform was used as anaesthetic and maintained that this was responsible for the arrhythmia After severing the vagi ectopic beats occurred less frequently or were absent (Kahn) This was confirmed by Nobel and Rothberger who also found that after vagotomy or the administration of atropine larger doses of epinephrine were necessary to precipitate ectopic beats and that they occurred less frequently It is probable that the sinus tachycardia resulting from vagotomy or the administration of atropine was one of the factors accounting for the rarer occurrence of the arrhythmia A direct depressant effect of atropine certainly also plays a part (*see* section on Atropine) Nobel and Rothberger also reported that during ether anaesthesia epinephrine caused ectopic beats in the dog whereas according to Meek and Seevers ephedrine does not have this effect in similar circumstances In this connexion too the part played by sinus tachycardia should be considered which in the case of ether results from peripheral vagal paralysis In Egmond s experiments on the automatically beating perfused heart of the dog no ectopic arrhythmias were observed but in his investigations the excitability of the heart can hardly be assumed to have been normal

In cats and rabbits premature beats were invariably seen after the administration of epinephrine (Petzetakis Schlapp) In the experiments of Hoff and Nahum on cats the intravenous injection of 0 1–0 2 mgm of epinephrine consistently caused ectopic beats which on repeated injections into the same animal always originated in the same focus they disappeared after vagotomy (confirming earlier observations discussed above) This effect of epinephrine is not due to a rise in blood pressure as it is still present if the pressor

effect is eliminated by an equalizer (Allen) Denervation of the carotid sinus or severing of the depressor nerves in dogs did not abolish the arrhythmia caused by epinephrine (Milles and Smith)

Ectopic beats could be elicited by epinephrine with greater constancy and in greater numbers if the animal had previously been sensitized by small doses of barium (Rothberger and Winterberg) In such experiments the action of epinephrine was akin to that of faradic *stimulation of sympathetic cardiac nerves An entirely different effect of epinephrine* was observed if the animal had previously been treated with aconitine in such small doses that except for the occurrence of extrasystoles no changes in cardiac function occurred in such circumstances extrasystoles in bigeminal rhythm invariably disappeared on stimulation of the sympathetic cardiac fibres and epinephrine had the same effect (Scherf unpublished observations) (*See also* chapter on Extrasystoles and the Nervous System)

According to Wegria and Nickerson epinephrine raises the fibrillation theshold in the dog

Epinephrine also increases the automaticity of excised strands of Purkinje tissue of the dog s heart as ascertained by microscopic observation (Ishihara and Pick Wachstein)

Regarding the effect of barbiturates on arrhythmias produced by epinephrine *see* section on Barbiturates (p 315)

Ephedrine

In dogs 5–10 mgm per kg given intravenously cause only slight changes in the T waves larger doses (20 mgm per kg) have a depressant effect on the specialized tissue (Chen and Meek) The latter mode of action which is characteristic for ephedrine is presumably the reason for the rare occurrence of dangerous arrhythmias in instances in which ephedrine is employed La Barre confirmed in cats the depressant effect of ephedrine in doses exceeding 20 mgm per kilo and did not see arrhythmias if doses up to 50 mgm per kilo were given intravenously to cats in deep chloroform anaesthesia According to Melville ephedrine unlike epinephrine never induces ventricular fibrillation during chloroform anaesthesia As mentioned above (p 317) ephedrine as distinct from epinephrine does not produce ectopic beats in dogs anaesthetized with ether Regarding the prevention by sodium barbital of ectopic arrhythmias resulting from ephedrine *see* section on Barbiturates (p 315)

Clinical Observations

The occurrence of extrasystoles is a common experience in patients who use epinephrine in the usual doses for such conditions as bronchial asthma allergic conditions etc If extrasystoles were already present before their number is increased by epinephrine Bourne investigated this subject in some detail by giving subcutaneously 1 cc of a solution of 1 1 000 to eighteen patients with persistent extrasystoles electrocardiograms were taken for one minute every five minutes The results were uniform about five minutes after the injection the number of extrasystoles increased considerably for thirty to sixty minutes while the increase in the heart rate was slight Patients with auricular extrasystoles developed ventricular ones and vice versa additional centres of ectopic impulse formation being activated by the drug According to Frey 0 3 mgm of epinephrine injected into normal subjects elicited extrasystoles in 9 per cent

Intravenous injections even of fractions of 1 mgm often cause extrasystoles (Hoffmann Danielopolu and Danulescu 1921 Smith and Moody de Graff and Weiss Otto) That of 1 mgm may precipitate dangerous extrasystolic arrhythmias and even fibrillation of auricles or ventricles (Gallavardin *et al* Hume) An unusual observation has been reported by Byrd in a patient anaesthetized with ether focal application of epinephrine was followed by severe arrhythmias and fall in blood pressure It is probable that the epinephrine and

not the ether was responsible for the accident since according to the author a large pack soaked with epinephrine in a 1 1 000 solution was applied to a bleeding area during the operation

In patients with A V block and Adams Stokes attacks due to transient ventricular fibrillation the administration of small doses of epinephrine may cause ventricular extra systoles (Roelsen) and ventricular fibrillation (Danielopolu and Danulescu 1916 Dock Schwartz and Jezer)

In patients with suprarenal tumours enhancement of impulse formation has been observed during hypertensive crises attributed to adrenaline circulating in the blood This seems to affect mainly impulse formation in the A V node with resulting A V rhythm and various forms of dissociated rhythms including dissociation with interference (Burgess Watermann and Cutts Hegglin and Holzmann Espersen and Jørgensen) In Hegglin and Holzmann s patient occasional ventricular extrasystoles were also observed during such crises

Quinidine and acetyl beta methylcholine abolish epinephrine extrasystoles (Hoff and Nahum Nathanson 1935 1936)

In addition to epinephrine other pressor amines were studied Veritol caused auricular or ventricular extrasystoles and short attacks of paroxysmal tachycardia in eight out of thirty patients (Aschenbrenner and Codas Thompson) Intravenous injection of paredrine also precipitated extrasystoles (Iglauer and Molle)

SUMMARY

It has frequently been demonstrated that pressor amines in particular epinephrine (adrenaline) cause ectopic beats and paroxysmal ventricular tachycardia in various species If the administration of such drugs was associated with chloroform or cyclopropane anaesthesia or if the animals had previously been given barium ectopic beats occurred in great numbers and such arrhythmias tended to develop into ventricular fibrillation If on the other hand aconitine had previously been given the ectopic beats were abolished by epinephrine Ephedrine owing to its depressant effect causes ectopic beats more rarely

Clinical observations are in accordance with the experimental ones even after the exhibition of small doses of epinephrine as they are commonly employed in clinical practice extrasystoles are frequently observed and auricular as well as ventricular fibrillation has occasionally been reported On the other hand epinephrine may also abolish extrasystoles this effect is not only due to tachycardia

The greatest caution is necessary if pressor amines are given during chloroform or cyclopropane anaesthesia

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STRYCHNINE

Though the use of strychnine in the treatment of extrasystoles has repeatedly been recommended its efficacy is doubtful and reports about its effect are conflicting

The idea of employing strychnine in this way seems to go back historically to the time at which extrasystoles were believed to be due to weakness of the heart muscle the arrhythmia indicating the difficulties of the heart muscle in contracting against aortic pressure

The extensive use which at one time was made of this drug on the continent of Europe as one of the three constituents of the then popular Wenckebach pills (which contained quinidine sulph 0 04 gramme strychnin nitrat 0 0006 digitalis (powdered leaves) 0 02 gramme *see* section on Treatment p 477) was due to Wenckebach who credited his English friends with having given him this suggestion (Wenckebach 1938)

Experimental

According to Smith (1917) in the heart of frogs and rabbits strychnine acts as a depressant and retards the occurrence of arrhythmias due to aconitine ouabaine and coronary occlusion From these experiments which do not appear to have been repeated Smith concluded with the greatest reserve that strychnine may have a place in the treatment of ectopic beats

Clinical Observations

In a critical review on the action of strychnine in heart failure Parkinson and Rowlands arrived at the conclusion that there is no justification for the use of this drug

For the treatment of extrasystoles several investigators found strychnine effective (Walsh Fahr) Carter and Traut used a combination of 3 grains of quinidine sulphate and 1/30 of a grain of strychnine sulph In a sixty year old patient with frequent extrasystoles neither digitalis nor quinidine or strychnine alone in the above doses proved satisfactory The best effect on the extrasystoles was achieved when quinidine and strychnine were given combined

In a case of aortic regurgitation with extrasystoles strychnine repeatedly abolished the premature beats which recurred whenever the drug was discontinued As no other drug was given this is perhaps the most convincing observation of a beneficial effect of strychnine on extrasystoles (Wenckebach)

On the other hand Smith (1924) reported two instances in which strychnine precipitated extrasystoles

CONCLUSIONS

The number of controlled observations on the effect of strychnine on extrasystoles is too small to warrant any definite views The impression obtained by perusal of the relevant literature is that the efficacy of strychnine in the treatment of such arrhythmias is highly questionable

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CAFFEINE

Experimental

It may be of some historical interest to mention that as early as 1872 Aubert reported arrhythmias in dogs following the intravenous injection of 0 1 gramme of caffeine Since only blood pressure tracings were recorded the kind of arrhythmia could not be analysed Aubert quoted older observations of Lehmann regarding irregular and intermittent pulse in man after ingestion of 0 3–0 6 gramme of caffeine

Following the administration of caffeine Pilcher observed ectopic beats in dogs *but not* in cats Beattie Brow and Long and Dikshit who reported their occasional occurrence in cats as a result of caffeine showed that they were due to a direct action of this drug upon the hypothalamic centres In earlier experiments in dogs carried out on the perfused heart

in situ in which complete A V block had been produced Egmond found that caffeine precipitated ectopic beats which gradually increased in number the arrhythmia culminating in an attack of ventricular tachycardia In these experiments a direct action on the cardiac centres has also to be assumed

Clinical Observations

That the consumption of coffee or tea may produce extrasystoles is a common clinical experience and in many textbooks these beverages are rightly mentioned as important and frequent causes of extrasystoles Some reports of these irregularities then described as intermittent pulse can be found in writings published long before the modern classification of arrhythmias (for example Stokes 1854 Lorain 1870 Riegel 1877) Mackenzie described a case in which extrasystoles occurred after every cup of tea consumed Even the time of day at which tea is taken may determine whether or not extrasystoles are precipitated (*see* section on Treatment p 473) The disappearance of the ectopic beats once the beverage is discontinued demonstrates that in such cases it actually was the cause of the arrhythmia

Very occasionally caffeine seems to exert the reverse effect that is abolishes ectopic beats Such an observation was reported by Barton regarding caffeine sod citr given in doses of 3 grains thrice daily

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NICOTINE

Experimental

Reports about the effect upon ectopic impulse formation of nicotine are conflicting According to Clerc and Pezzi the intravenous injection of 0 1–0 2 mgm per kg of nicotine in dogs occasionally causes ectopic beats which usually are auricular in origin In one experi ment a bigemina rhythm and on one occasion trigeminy was observed In view of the rarity of spontaneous extrasystoles in dogs these findings may be of some significance Other investigators were unsuccessful in their attempts to elicit arrhythmias by nicotine in cold blooded animals or in the mammalian heart (Barry Frommel)

In experiments in which the animals were sensitized for the development of ectopic arrhythmias results were more consistent In dogs sensitized with barium Rothberger and Winterberg found that nicotine elicited such arrhythmias its effect resembling in this respect that of epinephrine or of faradic stimulation of the cardiac sympathetic Similarly A G Levy reported ventricular fibrillation in cats resulting from nicotine during light chloroform anaesthesia its occurrence was independent from any vagal mechanism

Clinical Observations

Reports about the occurrence of intermittent pulse after smoking and attributed to it go back a considerable time (Graves and Stokes 1827 Lorain 1870 Nothnagel 1876 Riegel 1877) Regarding the amount of smoking which is necessary to produce extrasystoles reports are conflicting (Grassmann Gallavardin Boas and Levy) On several occasions observations were reported in which extrasystoles occurred during smoking disappeared while it was discontinued to re appear again when smoking was resumed (Bickel Leconte)

By smoking two or three cigarettes Goodall could produce extrasystoles in himself and according to this observer during the First World War abuse of smoking seems to have been a recognized method of producing extrasystoles in order to evade military service Kulbs reported that smoking causes extrasystoles more frequently in young people while in the elderly it is more apt to produce anginal pain

In a study on fifty five cases on the effects of nicotine intoxication on the other hand Genkin Piskarew Serebrjanik and Braun observed auricular extrasystoles in only three and ventricular ones in two instances It is also noteworthy that in a recent electrocardio graphic study in forty six subjects (eighteen normals twenty four patients with coronary *four with peripheral vascular disease) on the effect upon the circulation of the intravenous* injection of 2 mgm nicotine bitartrate extrasystoles are not even mentioned (Boyle Wegria Cathcart Nickerson and Levy) If it is remembered that according to Wenckebach and Winterberg even the intention of smoking alone may occasionally precipitate extrasystoles it becomes evident that no general conclusions are justified about the part played by nico tine and smoking in producing arrhythmias which should be some comfort to inveterate smokers

SUMMARY

Experimental work on the effect upon ectopic arrhythmias of nicotine have not yielded uniform results Only in animals sensitized with various drugs does nicotine produce such disturbances of rhythm consistently Clinical observations have established that while smoking produces extrasystoles in *some* individuals its effect varies considerably in different cases and no constant relationship between smoking (or administration of nicotine) and extrasystoles has yet been demonstrated

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ACONITINE

There is hardly any other drug which experimentally is apt to produce cardiac arrhythmias so constantly as aconitine (Matthews Cash and Dunstan Cushny) In such experiments ectopic beats occurred a short time after the administration of minute doses of the drug soon followed by ventricular fibrillation

A detailed electrocardiographic study demonstrated such arrhythmias to be due to auricular or to ventricular multiform ectopic beats (Dasbach working in Einthoven s laboratory)

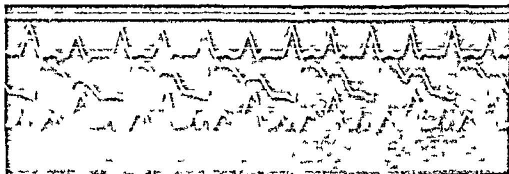


FIG 168 —From an experiment on a dog Tracings from above downward indicate suspension curves of right auricle and right ventricle electrocardiogram (ano o sophageal lead) time base 0 02 second Bigeminal rhythm owing to one ventricular extrasystole following each supraventricular beat produced by aconitine The extrasystoles have constant shape and accurate coupling

Subsequently it was shown in dogs that with careful intravenous administration of aconitine and repeated vagal stimulation bigeminal heart action persisting for over one hour could be produced with great constancy The bigeminy was due to extrasystoles auricular or ventricular in origin which in the electrocardiogram showed constancy of shape and of coupling (Scherf 1929) This method made it possible experimentally to study for the first time this kind of arrhythmia so common in clinical practice and generally so difficult to produce in experimental work (*See also* chapters on Nervous System and on Coupling) Extrasystoles elicited in this way are reproduced in Fig 168 and Fig 124 on p 195 These findings were confirmed by von Hueber and Lehr Extrasystoles caused by aconitine could be suppressed by the inhalation of a mixture of 20 per cent CO_2 and 80 per cent O_2 (Scherf 1930)

More recently it has been established that focal application of 0 05 cc of a 0 05 per-cent solution of crystalline aconitine in the form of a subepicardial injection into the dog s auricle is followed by a prolonged regular auricular tachycardia with a rate of about 200–300 per minute Cooling of the site of injection or its separation by clamping from the rest of the heart invariably abolished the tachycardia which re appeared when the interference was discontinued (Scherf 1947)

This auricular tachycardia showed a marked increase of rate during vagal stimulation and in rare cases auricular fibrillation developed If the same amount of aconitine was injected near the head of the sinus node into the *taenia terminalis* auricular fibrillation often appeared (Scherf Romano and Terranova) In these studies it was possible to produce auricular arrhythmias by aconitine without additional vagal stimulation either faradic or by vagomimetic drugs and they could thus be investigated without the complications inevitably created by additional interferences The result of these investigations also made it possible to form an opinion about the nature of such auricular tachycardias in particular whether they should be considered as paroxysmal tachycardia or as auricular flutter and seem to have an important bearing on the acceptance or rejection of the theory of circus movement as accounting for the mechanism underlying auricular flutter and fibrillation (*see* p 223)

That impulse formation in isolated strands of Purkinje tissue is enhanced by aconitine was shown by Ishihara and Pick and by Wachstein

Regarding the effect of the topical application of aconitine to the *ventricle* see sections on Flutter and Fibrillation p 232 and on Atropine p 333

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VERATRINE

Veratrine is a mixture of several veratrum alkaloids contained in various species of liliaceous plants Recent work has considerably advanced our knowledge of the chemical composition and biological action of individual alkaloids This whole problem has been comprehensively reviewed by Krayer and Acheson in 1946

Regarding the action of these compounds upon the circulatory system investigations were mainly concerned with their effect on blood pressure and heart rate whereas that on ectopic impulse formation has attracted less attention There are however several investigations the results of which have a bearing on the latter problem and which are pertinent in the context of this book This aspect may gain in importance in view of the recent revival of interest in treating hypertension with veratrum alkaloids

Experimental Investigations

Extrasystoles precipitated by veratrine in the frog s and mammalian heart have been reported by several authors but in many of such instances the reproduced tracings do not allow definite conclusions to be drawn or suggest alternative explanations

Seemann and Victoroff found Wuhlen of the frog s heart in the late stages of vera trine poisoning Their tracings show ectopic ventricular rhythms and some are suggestive of ventricular flutter and fibrillation Ectopic rhythms are also suggested by tracings of subsequent papers by this group of workers (Kretzer and Seemann Seemann) Wachstein optically recording the contraction of Purkinje fibres of the dog s heart interpreted his records as indicating bigeminal rhythm often with constant coupling of the smaller beat the extrasystoles displacing the dominant rhythm and sometimes being interpolated Gibert Queralto and Pescador recording in dogs electrocardiograms and suspension records reported extrasystoles with fixed coupling but their tracings can be better interpreted as

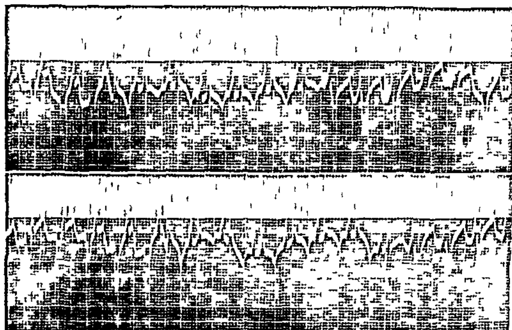


FIG 169 —From an experiment on a dog Lead 2 The two strips are con tinuous Parasystole between S-A rhythm and ectopic left ventricular tachycardia produced by the topical application of veratrine Note slow shift between the two rhythms and combination beats also absence of extrasystoles with accurate coupling For further explanation see text

showing ectopic ventricular rhythms Some records believed by those authors to demon strate bigeminal rhythms with extrasystoles occurring very late in diastole (prematurity of only 0 01 second) seem more likely to indicate alternation of intraventricular conduction

Soaje Echague found in dogs and rabbits that extrasystoles (usually multiform ventricu lar) occurred at the stage of hypertension but does not reproduce any tracings Terminal ventricular fibrillation was observed in dogs but not in rabbits

In strips of the left auricle of the heart of guinea pigs Rothberger and Sachs found that 0 7 mgm of veratrine in a 1 1 000 solution in divided doses invariably precipitated rhyth mic activity of high frequency, up to 360 but that this response was only transient and was soon followed by contracture If however by changing the nutrient fluid veratrine was removed at the start of such rhythmic activity this persisted up to four and a half hours arrhythmias being common Awakening of rhythmic activity by veratrine was also found in strips of ventricles of the turtle s heart (Rosenblueth *et al*)

There is therefore no doubt that veratrine alkaloids can precipitate ectopic rhythms The underlying mechanism is intimately related to the property of such compounds to increase and prolong the negative after potential The relation between negative after potential supernormal phase of recovery and repetitive response to single or continuous stimuli is discussed in more detail in the chapter on Mechanism Suffice it to say here that in connexion with veratrine such relations were established in nerve by Graham and Gasser Goldenberg and Rothberger showed in Purkinje fibres of dogs hearts that veratrine in higher doses produced abnormal rhythms very akin to tachycardic attacks whereby the rapid impulses followed an initiating beat during its greatly prolonged after potential their paper is discussed in some more detail in the chapter on Mechanism (p 502) Observations on the effect of veratrine upon nerve were also important in showing that the negative after potential though a very important factor is not the only one to account for supernormality Such findings are discussed in the review by Krayer and Acheson

None of the papers discussed have provided any evidence that in the heart extrasystoles in the strict sense of the term are produced by veratrine alkaloids Recently Scherf and Chick established in dogs that the *topical* application of veratrine (0 5 per-cent solution either applied to the epicardial surface of a ventricle by means of a small piece of filter paper or by subepicardial injection of 0 05 cc of the solution) produced parasystole with simple interference between sinus and an ectopic rhythm Fig 169 provides an example It shows parasystole with interference between S A and an ectopic left ventricular rhythm The sinus beats have slender high and peaked P waves which are easily identified followed by R waves which vary in height and inverted T waves The initial deflections of the ectopic beats have deep S waves which are followed by upright T waves The cycle length of the sinus rhythm is 0 40 second (rate 150 per minute) that of the ectopic rhythm 0 38 second (rate 158 per minute) Owing to the close proximity of the rates of these two rhythms a slow shift between them occurred Combination beats were also recorded for example the third and fourth but last complexes

The main difference between such experimental parasystole and that observed in clinical instances was that in the experimental variety the ectopic rate was much faster If several such parasystolic foci were produced in different portions of the heart interferences of several rhythms ensued It is of interest that extrasystoles with accurate coupling were never observed in these experiments this is the more noteworthy as true extrasystoles can readily be elicited by the topical application of digitalis or strophanthin that is by compounds with which veratrine has often been compared regarding some of its biological actions

Stutzman *et al* found in dogs anaesthetized with pentobarbital that the intravenous injection of 20–50 times the minimal effective dose of Veriloid produced *inter alia* transient A V rhythm and still larger doses ventricular tachycardia at 200–500 times the minimal dose a coarse ventricular fibrillation was occasionally observed In the unanaesthetized animal very high intravenous dosage produced similar effects except that ventricular fibrillation was never observed Such observations on Veriloid are of importance as this substance has recently been clinically employed in the treatment of hypertension Veriloid is a mixture of amorphous veratrum alkaloids obtained by fractionation and is biologically standardized according to its vasodepressor effect in dogs It does not contain several of the powerful identified alkaloids (Kauntze and Trounce 1951a)

Clinical Observations

In studies reported so far on the treatment of hypertension with Veriloid arrhythmias seem to play a small if any part amongst the numerous toxic manifestations of this drug (Kauntze and Trounce 1951a 1951b) If the use of this or similar veratrum compounds should become more widespread the recognition of their effect upon ectopic impulse formation may become important

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CHOLINE AND DERIVATIVES

Experimental Investigations

Of this group of drugs acetylcholine is the most important and most widely studied Regarding its action on the heart its direct stimulating nicotinic —as distinct from its parasympathomimetic muscarinic —effect has attracted increasing attention of late

Most of such investigations are concerned with the effect of acetylcholine upon the con tractility Regarding studies on the effect of this compound and its derivatives upon ectopic rhythms which alone are relevant in the present context data are available which tend to show that they may suppress as well as precipitate such arrhythmias

A pronounced *inhibitory* effect of acetyl beta methyl-choline upon ventricular rhythms produced by adrenaline has been established by several authors (Hoff and Nahum Nath anson 1935 1936)

The *stimulating* effect has attracted increasing attention in connexion with the role played by acetylcholine in the transmission and initiation of impulses in various tissues (for ex ample sympathetic ganglia Bronk sensory nerve endings Gray) In the heart such stimulating effect has been reported in a variety of experimental conditions

If in experiments on dogs with the heart *in situ* such small doses of aconitine were in jected that no changes in the electrocardiogram occurred the intravenous injection of choline or acetylcholine precipitated extrasystoles This effect was not abolished by atropinization (Scherf 1929 *see also* section on Aconitine and chapter on Nervous System) A stimulating effect upon ectopic impulse formation in the dog s heart was also seen by Hall by Noth Essex and Barnes and by McDowall also by Goldenberg and Rothberger in isolated Purkinje fibres and by Garcia Ramos and Rosenblueth in the isolated appendage of the dog s auricle

The starting point of Burn s studies on the stimulating effect of acetylcholine was the

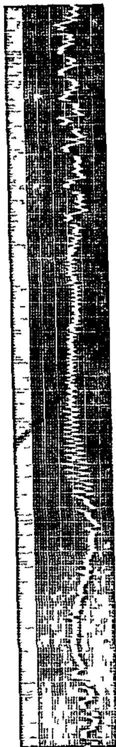


Fig 170.—From an experiment on a dog Auricular flutter and fibrillation immediately precipitated by the topical application to the sinus node of acetylcholine during vagal stimulation Note in the beginning of the record the inhibiting effect upon A V conduction of the vagal stimulation before acetylcholine was subsequently applied by means of a filter paper moistened with a 5 per cent solution

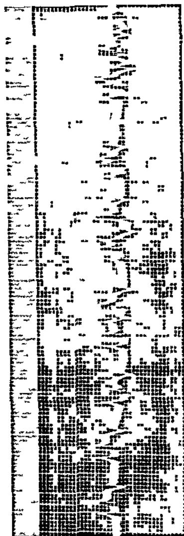


Fig 171.—From an experiment on a dog weighing 12 kg five minutes after the intra venous injection of 1 [illegible] mgm of atropine sulphate Auricular extrasystoles precipitated by the local application of a 5 per cent solution of acetylcholine to the sinus node of the heart *in situ* Lead 2



Fig 172.—From an experiment on a dog Auricular fibrillation precipitated by slight stretching of the auricular appendage after atropinization and subsequent topical application of acetylcholine to the sinus node of the heart *in situ*

observation that in the spontaneously beating auricle of rabbits paludrine inhibited the contractions which were then stimulated by acetylcholine paludrine reversed the usually depressant effect of this compound (Burn and Vane) The same change could be demonstrated without paludrine by allowing the auricles to beat until they were exhausted and contractions ceased after twenty four to thirty six hours at this stage addition of acetylcholine caused contractions to occur again and further addition of the substance strengthened them (Bulbring and Burn) This was interpreted as indicating that contractions can only occur as long as the tissue is capable of synthesizing acetylcholine This view was strongly supported by the observation that acetylcholine added to powder prepared from *fresh* auricles *depressed* the synthesis whereas added to the powder prepared from *exhausted* (stopped) auricles *augmented* it There was thus a clear relationship between contraction and synthesis and between change in activity and change in synthesis

Burn (1950) put forward the suggestion that just as in skeletal muscle acetylcholine is liberated by the nervous impulse so in cardiac muscle the mechanism for firing off the contraction is also acetylcholine but instead of being liberated by a nervous impulse it is synthesized and causes a contraction probably when a certain concentration is reached It is possible that the pacemaker controls the rate of beating by controlling the rate at which this concentration is reached These considerations may well have a bearing on the mechanism underlying the ectopic impulse formation in parasystole

In Nahum and Hoff s experiments on dogs application to the area of the sinus node of acetyl beta methylcholine caused auricular fibrillation in some instances and did invariably so if in addition the auricles were stimulated mechanically Scherf and Chick investigating also in dogs the effect of acetylcholine applied topically to the auricles and ventricles made the following observations Application of a 5 per cent solution of acetylcholine to the area of the *sinus node* caused immediate auricular flutter or fibrillation (Fig 170) this was invariably abolished by atropine Acetylcholine applied in this way after atropinization no longer precipitated auricular fibrillation but transient auricular tachycardia or auricular extrasystoles (*see* Fig 171) But for about ten minutes after the application of acetylcholine the auricles were extremely irritable and the slightest mechanical stimulus provoked fibrillation This is illustrated in Fig 172 obtained in another experiment in which acetylcholine had been applied already three

times with the same result as that shown in Fig 170 Then atropine sulphate (0 1 mgm per kg) was injected intravenously and acetylcholine applied locally once more to the sinus node After the first few beats shown in Fig 172 the right auricular appendage was slightly stretched this produced an immediate increase in rate of the prevailing sinus rhythm quickly followed by auricular fibrillation

Application of acetylcholine to the *ventricles* in the non atropinized animal caused transient regular ectopic ventricular tachycardia and on the whole the response of the ventricles to the topical application of acetylcholine was similar to that of the auricles

As distinct from the topical application of acetylcholine after its systemic application and complete atropinization mechanical or electrical stimuli applied to the ventricles precipitated temporary parasystolic arrhythmia whereby ectopic beats occurring in groups were also observed (Scherf Chick Scharf and Terranova) This has to be considered as another variety of a stimulating effect of this drug on ectopic impulse formation

The mechanism underlying such stimulating effect of acetylcholine on impulse formation is little understood Much work on this topic is in progress and any views on this subject can only be considered as provisional and largely hypothetical

Acetylcholine has been reported to shorten the chronaxie of the frog s ventricle (Frederícq) Hoffmann and collaborators demonstrated by several pharmacological tests the presence of an epinephrine like substance in the perfusate of the isolated heart of several mammalian species after acetylcholine was liberated or nicotine injected into the heart These authors consider the possibility that such release takes place in certain nervous structures of the heart and that such mechanism may have a bearing on vagal escape and on the accelerating effect of vagal stimulation after atropinization and after sympathectomy McNamara and co workers showed in the isolated heart of rabbits that the cardiovascular stimulation produced by acetylcholine is potentiated by calcium and attribute it to the release of a sympathomimetic substance possibly epinephrine While these experiments demonstrate possible links between the stimulating action of acetylcholine and of adrenaline it has to be borne in mind that these relationships are complex topical application of epinephrine in a concentration of 1 1 000 and 1 10 000 following intravenous injection of 0 01 gramme of acetylcholine in the atropinized dog did not produce ectopic rhythms (Scherf and Chick)

There is reason to assume that the suppression of ectopic rhythms by quinine and cocaine compounds may be due to their inhibitory effect on the liberation of acetylcholine (*see* Dawes 1946 Burn 1950 Feldberg 1950)

In sympathetic ganglia there seems also to exist some relationship between acetylcholine deficiency failure of transmission of excitation and spontaneous activity in the form of repetitive discharge If the stellate ganglion was perfused with a solution deficient in calcium it was observed that the cells discharge spontaneously at a time when synaptic transmission is blocked In several experiments we have observed during the early stages of low calcium the development of repetitive after discharge following each preganglionic volley (Bronk *et al* 1938) This was confirmed by Harvey and MacIntosh and attributed to failure of acetylcholine to appear in active concentration While observations made on one kind of tissue cannot be applied to another without the greatest reserve these observations are quoted to draw attention to the simultaneous presence of a state of blocked transmission of impulses and enhanced spontaneous impulse formation in which acetylcholine deficiency seems to play a part and which may well have a bearing on the mechanism underlying parasystole (*see* chapters on Pararrhythmias and on Mechanism)

Clinical Observations

At one time choline and related substances were used for the purpose of stopping attacks of paroxysmal tachycardia (Boden and Wankell Starr Morgan) but in view of the

unpleasant side effects this method of treatment is now seldom used In man too this group of drugs may precipitate ectopic beats (Boden and Wankell Schliephake Segers *et al*) and this accords well with the analogous experimental findings that choline and derivatives may cause as well as abolish ectopic arrhythmias

Recognition of the stimulating effect of acetylcholine on ectopic impulse formation is of clinical interest as it affords an understanding of certain observations often termed paradoxical They include for example the occurrence of ventricular and auricular beats and tachycardias during carotid sinus pressure and of ectopic arrhythmias in other circumstances associated with vagal stimulation

Appreciation of the dual mode of action of these substances is of clinical importance as they are widely used in various clinical conditions

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ATROPINE

The effect of atropine upon cardiac irregularities generally has extensively been studied experimentally as well as clinically Such investigations were performed long before any thing like a modern classification of arrhythmias had been established The great interest which this subject aroused at such an early stage is easily understood if the exaggerated view of the importance of the nervous system in the production of arrhythmias is remembered as it was prevalent in those days In this connexion Heidenhain s paper of 1872 is of interest as it illustrates the line of thought current at that period he investigated the effect of atropine on arrhythmias caused by direct stimulation of the medullary centres and found that they were abolished by the drug Heidenhain interpreted this observation as indicating that premature contractions were due to high vagal tone Similar views regarding the abolition by atropine of milder degrees of intermittency were still current at the end of last century (Dehio) The part played by the tachycardia with its resulting shortening of diastole or a direct effect of atropine on stimulus formation could not be appreciated at that time

Experimental

Nobel and Rothberger found in dogs anaesthetized with chloroform that after the administration of atropine larger doses of epinephrine were necessary to elicit ectopic arrhythmias (*see also* sections on Chloroform and on Epinephrine) Ventricular extrasystoles produced in dogs by aconitine were abolished by atropine (Scherf 1929 *see also* section on Aconitine) It could be shown that this effect was not due to the increase in the sinus rate as extrasystoles remained absent if the sinus rhythm was slowed by cooling the sinus node A transient increase in the number of extrasystoles before their disappearance was also observed occasionally In more pronounced disturbances of rhythm caused by aconitine atropine was without effect

Of interest is the observation that after atropinization topical application of aconitine crystals to the ventricles of the exposed heart of dogs does not lead to ventricular fibrillation whereas without atropine ventricular fibrillation invariably occurs after a ventricular tachycardia This experience also suggests a direct action of atropine upon the myocardium since direct vagal effects cannot be assumed to exist in the ventricles

In this connexion an observation made by Winterberg as early as 1908 is of interest namely that the administration of atropine makes it impossible subsequently to elicit auricular fibrillation by faradic stimulation of the auricles

Auricular fibrillation caused in the dog by focal application of aconitine to the auricular surface of the heart *in situ* invariably disappeared after the intravenous injection of large doses of atropine (Scherf 1949) This was attributed to lengthening of the refractory period of the auricle

Clinical Observations

The suppression of extrasystoles by atropine in man has repeatedly been reported (Robinson and Draper Halsey Danielopolu and Proca 1925 Marchal and Heim de Balsac) Sometimes large doses of atropine were given for the purpose as much as 3 6 mgm (Michailoff and Solitermann)

Gold and Otto reported that in five patients with bigeminal heart action due to digitalis *4 mgm* of atropine given hypodermically in a single dose reduced the number of extrasystoles which finally disappeared altogether

In a series of eleven cases Bourne gave atropine subcutaneously (grain 1/50) In ten of these the number of extrasystoles diminished after the injection while at the same time the heart rate became slower for about four minutes as the result of the initial vagal

stimulation by atropine This observation demonstrates that the reduction in the number of extrasystoles could not have been due to a shortening of diastole (*see* also chapter on Nervous System)

The importance of atropine in preventing arrhythmias during cyclopropane anaesthesia is stressed in a more recent paper by Rink Helliwell and Hutton It is based on obser vations in forty two patients operated for the relief of congenital pulmonary stenosis Most of them were children Pre medication consisted of a full basal narcosis with nembutal (½ grain per 14 lb body weight) and atropine grain 1/100 Regarding the importance of atropine these authors wrote Cardiac irregularity has likewise not been frequent and has been easily mastered by a brief period of substituting ether This relative immunity from bradycardia and irregularity we ascribe to the use of a full dose of atropine in Blalock s own practice where much smaller doses were given both these phenomena caused concern and had frequently to be corrected by a further dose administered intravenously

While the effect of atropine in suppressing or preventing extrasystoles is established occasionally the reverse action was observed namely that the administration of atropine elicited extrasystoles (Luten Scott Fogelson) In Danielopolu s case (1914) concerning a patient with occasional auricular extrasystoles atropine precipitated continuous bigeminy due to auricular extrasystoles Galli reported an observation in which an attack of paroxys mal tachycardia occurred after atropine had been given orally as well as intravenously Danielopolu and Proca claimed that ocular pressure rarely precipitated extrasystoles unless atropine had previously been given

The validity of a test suggested by Leconte to distinguish between functional and organic extrasystoles by the effect upon the ectopic beats of atropine seems questionable

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PAPAVERINE

Experimental

Rossler investigating the effect of papaverine on the dog s heart (Starling preparation) found an increase in contractility According to Elek and Katz in larger doses this com pound is a cardiac depressant These authors also found lengthening of the refractory period of auricles and ventricles and after intravenous injections of doses varying between 92 and 845 mgm per kg observed in dogs disturbances of conduction multifocal ectopic beats and paroxysmal ventricular tachycardias In therapeutic doses papaverine raises the fibrillation threshold (Lindner and Katz Wegria and Nickerson) The mortality of dogs after ligation of coronary branches was found to be reduced by over 50 per cent as the result of prior administration of papaverine (McEachern Smith and Manning)

Clinical Observations

In an early clinical study on the therapeutic uses of papaverine Pal (1914) observed the disappearance of extrasystoles

More recently Katz and Elek reported that in twelve patients with numerous extra systoles the intravenous injection of 0 06–0 1 gramme of papaverine reduced their number considerably sometimes abolished them altogether When this drug was given by mouth in doses of 0 1-0 2 gramme four or five times daily a definite reduction in the number of extrasystoles was observed the efficacy of papaverine being comparable in this respect to that of 0 2 gramme of quinidine given four or five times daily This effect on extra systoles of papaverine was not confirmed by Laake

The intravenous administration of larger doses of papaverine to patients with damaged hearts is by no means free from risk We saw two patients die suddenly a few minutes after two intravenous injections each of 0 06 gramme of papaverine had been given in quick succession It is too readily forgotten that the experimental observations discussed above were obtained on normal hearts whereas clinically the drug is usually given to patients whose heart is anything but normal

SUMMARY

The effect of papaverine in suppressing extrasystoles is a useful property of this drug which however should never be given with the sole purpose of abolishing extrasystoles

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AMYLNITRITE

Experimental

In experiments on dogs Halsey found that ectopic beats caused by digitalis or strophanthin disappeared for a short time after the inhalation of amylnitrite In one experiment however in which digitalis failed to produce such arrhythmia ectopic beats were precipitated by amylnitrite and persisted for 90 seconds

Clinical Observations

In subjects prone to extrasystoles at certain times amylnitrite—in doses commonly used for the relief of anginal pain—is apt to elicit the arrhythmia This effect is so frequent that it can be employed as a diagnostic test in cases in which the patient gives a history suggestive of extrasystoles but does not exhibit any premature beats on examination—an occurrence which is by no means rare (*see* section on Incidence) (Scherf) In such instances extrasystoles are usually observed a few minutes after the inhalation of amylnitrite during the height of the drug effect they are not present since the tachycardia which is an immediate but transient effect of the inhalation with its ensuing shortening of diastole prevents their occurrence In this respect the action of amylnitrite is analogous to that of exercise The most likely mechanism underlying this effect of amylnitrite is the pronounced fall in blood pressure with its resultant changes in the tone of autonomic nerves

In subjects in whom extrasystoles were present before the inhalation their number is often increased (Bourne) and inhalation for 15–20 seconds may even cause short attacks of paroxysmal tachycardia (Scherf Scherf and Weissberg)

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SODIUM

The importance of the inorganic constituents of the perfusion fluid for the rhythmicity of the heart has been appreciated since Ringer s classical investigation in 1880

Regarding the part played by sodium while a general discussion of this subject is outside the scope of this book brief references may be made to a few papers emphasizing its importance for stimulus formation in the heart

More than fifty years ago Greene found in strips of the apex of the terrapin s ventricle that upon its immersion into a hypertonic solution of NaCl rhythmic contractions started after a very short latent period According to Kisch sodium salts in higher concentrations applied to the sinus node of frogs hearts have no influence upon impulse formation but Andrus and Carter found that substituting a 2 per-cent solution of NaCl for Ringer s solution precipitated ectopic beats Baetjer and McDonald analysed in greater detail the mechanism of the effect upon impulse formation of the sodium ion in its interaction with potassium and calcium and Carlson that of isotonic NaCl solution on the heart of limulus

In the dog s heart *in situ* the effect upon impulse formation of the focal application of hypertonic solutions of NaCl to the cardiac surface was investigated electrocardiographically

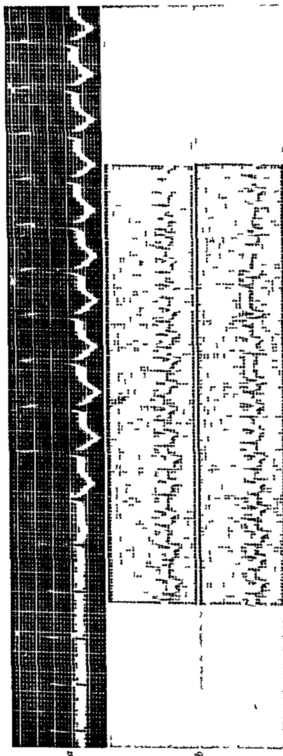


Fig 173 —From two different experiments on dogs *a* The beginning of ventricular tachycardia 12 seconds after brushing a 10 per cent solution of NaCl on the conus area of the right ventricle *b* The two strips are continuous Auricular extrasystoles and short paroxysm of auricular tachycardia after application of a 5 per cent solution of NaCl to the tail of the sinus node

by Piccione and Scherf A 5 10 or 30 per-cent solution was brushed on a small area of the surface of an auricle or ventricle or 0 1 cc of a 10 per-cent solution was injected subepicardially By either method was it possible to elicit extrasystolic arrhythmias but the latter produced the irregularities more constantly and more readily and they occurred far more frequently in the ventricles than in the auricles Such arrhythmias started within a few seconds of the interference and disappeared within a few minutes

Fig 173 illustrates such observations Fig 173a shows the beginning of a paroxysm of ventricular tachycardia which started twelve seconds after brushing a 10 per cent solution of NaCl on the conus area of the right ventricle Such tachycardias were regular and came on much sooner after the application than the irregular tachycardias which were observed after the application in a similar way of barium salts This is one of several observations which tend to show that the effect of NaCl is a specific ionic effect of sodium and not due either to the mechanical stimulation by the application or injection or to the osmotic pressure of the hypertonic solution Fig 173b taken from another experiment shows numerous auricular extrasystoles and a short paroxysm of auricular tachycardia following the application to the tail of the sinus node of a 5 per-cent solution of NaCl In the last part of the tracing blocked auricular extrasystoles from another centre were recorded one of which can be seen during the attack of tachycardia

By the same method auricular or ventricular bigeminy and trigeminy could be produced

An important feature of such arrhythmias is that the coupling of the extrasystoles was always constant in any given experiment This suggests that the ectopic beats originated in the same circumscribed focus where they were precipitated by the preceding beat that is they were extrasystoles in the strict sense of the term This view is supported by the observation that warming by means of a thermode of the site of application of the NaCl solution invariably increased the number and the rate of the extrasystoles or caused them to occur in those instances in which injection alone had failed to elicit them (Scherf) This last observation warrants the conclusion that the site of application of the hypertonic solution was the site of the focus giving rise to the ectopic beats

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POTASSIUM

Experimental

Generally potassium salts are cardiac depressants The antagonistic action of the K ion to Na and Ca has been known for a long time (Ringer Lingle Kisch 1926b) and while to a certain extent such antagonism applies also to their effects on ectopic impulse formation it will be shown that the mode of action of potassium salts in this respect is rather complex

At first the effect upon the heart action of potassium salts was thought to consist in

producing cardiac standstill (Blake 1839 Traube 1864 Guttmann 1866 Boehm 1877 Braun 1904) but at an early stage it was recognized that the resulting condition actually was ventricular fibrillation (Aubert and Dehn 1874) Subsequent investigations emphasized the complexity of the potassium effect on cardiac activity

It was shown by Gross (1903) that the mode of action of potassium salts depended *inter alia* on whether they were applied to the isolated heart or to the animal with the heart *in situ* in the former event it produced cardiac standstill in the latter ventricular fibrillation The results of Hering s experiments published in the same year pointed in the same direction he demonstrated that ventricular fibrillation induced in the isolated mammalian heart by various agents was *abolished* by the administration of potassium after its removal rhythmic contraction set in again These findings were confirmed by Mathison and by Wiggers (1930a) In a later series of experiments Hering (1915) emphasized the differences between the isolated heart and that *in situ* regarding its reaction to potassium intravenous injection of 4 cc of a 1 per cent solution of KCl *precipitated* ventricular tachycardia in rabbits and ventricular fibrillation in dogs

An inhibitory action upon ectopic rhythms of potassium salts was found by McCord Hofmann Kolm and Pick and regarding isolated Purkinje fibres by Ishihara and Pick

It was thus demonstrated that the systemic application of potassium salts may precipitate as well as inhibit ectopic arrhythmias and that one of the factors responsible for this seemingly contradictory effect of the salts was whether they had been applied to the isolated heart or that *in situ* Others were the concomitant exhibition of other drugs and dosage

Regarding the former of these it was established by Scherf and confirmed by Hueber that in dogs treated with such small doses of aconitine that the electrocardiogram remained unchanged the intravenous injection of 0 005–0 05 gramme KCl invariably elicited ventricular extrasystoles with accurate coupling and ventricular tachycardia Such arrhythmias disappeared within a few minutes and could be brought out again by a renewed injection of KCl In this connexion it is noteworthy that in Hering s experiments of 1915 quoted above prior to the administration of KCl delphinine had been employed which according to unpublished observations (Scherf) exerts upon ectopic impulse formation an effect similar to that of aconitine

Dosage was established as a further important factor to account for the paralysing or stimulating effect respectively upon ectopic impulse formation of potassium salts

Wiggers (1930a) as already mentioned reported the abolition by KCl of ventricular fibrillation caused in various ways In such experiments on cats and dogs he injected 50 mgm (1 cc of a 5 per cent solution) per kg into the ventricular cavities In further investigations (Wiggers 1930b) he established that smaller doses—for instance the fast intravenous injection of 30–100 mgm—had in dogs the reverse effect namely elicited ventricular fibrillation Wiggers explained the last finding by the assumption that such smaller doses produce disturbances of conduction causing the setting up of islets of refractory tissue and resulting in circus movement of the excitation wave without inhibition of stimulus formation If on the other hand doses of not less than 50 mgm per kg are injected intravenously the excitability of the whole heart is diminished impulse formation as well as conduction being affected and the result is cardiac standstill If it is desired to abolish ventricular fibrillation the potassium salt should preferably be injected simultaneously into both ventricles

Ventricular fibrillation caused by potassium shows certain characteristic features differentiating it from ventricular fibrillation caused by other means (Wiggers)

The importance of the dosage and also of the speed of administration of KCl regarding the resulting effect upon ectopic arrhythmias is evident from Nahum and Hoff s investigations In rabbits the intravenous injection of 1–3 cc of a 10 per-cent solution of KCl caused ventricular fibrillation within one or two minutes On the other hand that of 30–50

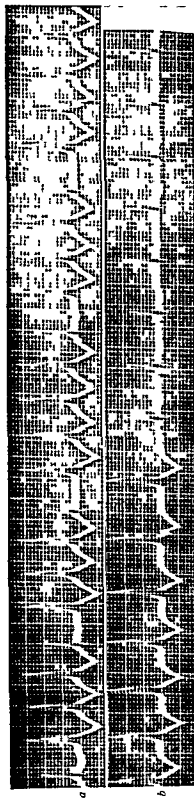


FIG 174—From an experiment on a dog a Extrasystolic arrhythmia elicited by the topical application of sodium chloride to the conus of the right ventricle b Suppression of the ectopic rhythm by the topical application of potassium chloride to the same area For further explanation see text

cc of a 1 per cent solution given at a rate of 1–2 cc per minute was followed in rabbits and cats by a diminished rate of stimulus formation disturbances of conduction and cardiac standstill without any ectopic impulse formation being observed The ventricular fibrillation caused by the rapid injection was attributed to disturbances of conduction occurring before depression of impulse formation had become manifest—a conception very similar to that of Wiggers discussed earlier

Chamberlain Scudder and Zwemer found in cats that slow intravenous injection of potassium salts was followed first by ventricular ectopic beats then by ventricular paroxysmal tachycardia and finally by ventricular fibrillation The various arrhythmias corresponded to different blood levels of potassium

As distinct from the *systemic* administration of potassium salts discussed so far their *topical* application has on the whole only a depressant effect

According to Kisch topical application of potassium salts to the sinus node of the frog s heart causes increase in the rate of impulse formation this was found to be more pronounced if previous manipulations had resulted in a slowing of rate (Kisch 1926a)

With a similar method Hofmann found in the mammalian heart that topical application of potassium chloride (1 per cent) caused inhibition of stimulus formation in the sinus node

In the dog topical application of a 5 per cent solution of KCl to the area of the sinus node or to different areas of the ventricular surface never produced premature or ectopic beats (Boyd and Scherf) On the contrary if such arrhythmias had been produced by means of sodium or barium applied topically by the same technique subsequent application of KCl to the same area abolished them immediately (Piccione and Scherf) This is illustrated in Fig 174

Fig 174a shows series of three or more extrasystoles occurring in succession which had been elicited by brushing a 10 per-cent solution of NaCl on to a small area (4 mm diameter) of the conus of the right ventricle The first extrasystole of such series was accurately coupled to the preceding beat Subsequent application of a 5 per-cent solution of KCl to the same area

first slowed the ectopic rhythm and then abolished the extrasystoles (Fig 174b) Similar results were obtained in regard to ectopic beats precipitated by the topical application of digitalis (Scherf unpublished observations) If by the sub epicardial injection of 0 05 cc of a 0 05 per cent solution of aconitine into the area of the sinus node auricular flutter or auricular fibrillation had been elicited injection into the same area of 0 05 cc of a 1 per cent solution of KCl restored sinus rhythm immediately (Scherf and Terranova)

Clinical Observations

Clinical observations are in accordance with those made experimentally that potassium may abolish as well as precipitate ectopic arrhythmias Thus extrasystolic arrhythmias have been observed in clinical conditions associated with hypopotassemia for example bigeminal pulse during hypokalaemia in an attack of induced periodic paralysis (Gass *et al*) auricular extrasystoles in two out of thirty two cases of post operative potassium deficit (Eliel *et al*) and ventricular bigeminy with low serum potassium during p amino salicylic acid treatment (Cayley) On the other hand ectopic arrhythmias have been reported in patients with hyperkalaemia (Somerville Levine Merrill and Somerville) The complex mode of action upon the heart of the potassium ion was stressed by Levine *et al*

The inhibitory effect upon ectopic impulse formation of potassium salts has been employed in clinical practice for abolishing extrasystoles A few relevant observations may be briefly discussed

In fifty eight patients with auricular or ventricular extrasystoles Sampson and Anderson studied the effect upon the arrhythmia of various potassium salts they included bromide iodide acetate chloride and citrate In twenty nine cases a definite reduction in the number of extrasystoles was observed in ten the results were doubtful and in sixteen no effect was seen Three patients responded by an increase in the number of extrasystoles one of whom developed an attack of ventricular paroxysmal tachycardia The effective dose varied between 1 and 16 grammes a day in different individuals It took between forty and ninety minutes for a single oral dose to produce an effect which lasted for between three and eight hours In older patients and those with structural heart disease the smaller doses proved effective In those cases in which no effect was observed inadequate dosage or impaired absorption could be excluded as high potassium levels in the serum were found Untoward effects consisted in abdominal cramps and diarrhoea of the various salts the acetate caused the least gastro intestinal disturbance Renal disease is a contra indication against this form of treatment since impaired kidney function may result in dangerously high blood levels of potassium Potassium salts should only be given under medical supervision

Similar beneficial effects in the treatment of extrasystoles by potassium salts were seen in four cases of spontaneous extrasystoles (Castleden) and in thirty one patients with digitalis extrasystoles in whom 5–10 grammes of potassium acetate daily abolished the extrasystoles in every case (Sampson Alberton and Kondo) Good results of potassium salts (2 to 10 grammes of the chloride or of a chloride acetate mixture) were seen also by Enselberg and collaborators in cases of ectopic arrhythmias most of them due to digitalis The suppression of extrasystoles invariably achieved by this method in one patient during insulin hypoglycaemia was explained by the fall in serum potassium resulting from insulin (Aitken Allott Castleden and Walker)

The intravenous administration of potassium salts in man causes immediate death unless very small doses are given very slowly (Howard and Carey)

The occurrence of digitalis extrasystoles in failing hearts may in some instances be due to a diminished amount of potassium in the cells

SUMMARY

In experimental work it has been established that potassium salts may abolish as well as precipitate ectopic arrhythmias The factors responsible for the kind of action are not fully understood The effect was found to depend *inter alia* on whether the salts were applied to the isolated heart or to the animal with the heart *in situ* on the concomitant employment of other drugs the speed of injection and on the dosage used Topical application of potassium salts by means of brushing KCl solution on circumscribed areas of the exposed heart or by sub epicardial injection have almost exclusively a depressant effect on such arrhythmias

Clinical observations have shown that ectopic arrhythmias are found in association with hypo as well as hyper potassemia Potassium salts have a limited value in the treatment of extrasystoles The effective dose varies greatly in different individuals Their effect is not constant and in some cases they may precipitate ectopic arrhythmias Renal disease is a contra indication against the use of potassium salts which in any case, are much inferior to other drugs (for example quinidine) and which should only be given under medical supervision *See also* section on Treatment

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CALCIUM

Whereas the importance of the calcium ion for maintaining *normal* impulse formation has been firmly established since the classical work of Ringer Lingle Howell a o its effect upon *ectopic* impulse formation is far from clear Experimental as well as clinical obser vations are conflicting and much seems to depend on the species studied the dose employed and other drugs given in conjunction with it

Experimental

Stimulation as well as inhibition of ectopic impulse formation has repeatedly been reported a few examples may be quoted

On the isolated ventricle of the frog s heart Sakai found that small doses of calcium increased automatic rhythm whereas large ones had the reverse effect

Direct application to the sinus node of the frog s heart of calcium chloride in the lowest effective concentrations (m/100–m/75 $CaCl_2$) was found to inhibit normal impulse for mation higher concentrations (m/5 CaCl) increased it whereas still higher ones again resulted in inhibition If different concentrations of calcium chloride were topically applied to the ventricles the ectopic centres were affected in the same way here too small and large doses inhibited whereas medium doses enhanced impulse formation The latter effect manifested itself also by multiple responses of the heart to one mechanical stimulus Dif ferent results obtained by other investigators were explained as due to the use of different preparations and to differences in prior experimental interferences (Vorgeschichte des Praparates) (Kisch) In the isolated sinus of the terrapin s heart focal application of cal cium inhibited automaticity (Baetjer and McDonald)

In the mammalian heart the effect of calcium was found qualitatively similar to that of barium (in rabbits Frommel in dogs Rothberger and Winterberg Egmond) but larger doses of calcium were necessary to produce the same effects In Rothberger and Winter berg s experiments on dogs it was found that after the intravenous injection of 0 05 gramme

of calcium chloride simultaneous faradic stimulation of vagus and cardiac sympathetic was followed by ectopic ventricular beats With larger doses of calcium these occurred after stimulation of the sympathetic alone and still larger doses (0 1–0 2 gramme) precipitated ventricular tachycardias without any stimulation of cardiac nerves (These doses should be compared with those of barium employed in analogous experiments *see* section on Barium and chapter on Nervous System pp 347 and 254) The ectopic rhythms produced by calcium resembled those following administration of barium also in that the ectopic beats had varying coupling and varying shapes in the electrocardiogram bigeminal rhythms with accurately coupled extrasystoles were not observed Regarding the importance of this distinction *see* chapter on Mechanism

The intravenous injection of 1–2 cc of a 10 per cent solution of calcium chloride in dogs caused sinus bradycardia auricular fibrillation and disturbances of A V conduction (Hoff *et al* 1939) If larger doses were injected and concentrations of calcium in the serum of 30–65 mgm in 100 cc attained ectopic beats bigeminal rhythm ventricular tachycardia and ventricular fibrillation ensued Such abnormal rhythms could sometimes be suppressed by sodium amytal (Hoff and Nahum 1937)

Scherf on the other hand observed that extrasystoles produced by aconitine were suppressed by calcium given intravenously It should be remembered however that extrasystoles produced by aconitine respond in a paradoxical way to the stimulation of the cardiac sympathetic and of the vagus respectively (*see* chapter on Nervous System p 255)

Studies on the effect of calcium on the rhythmicity of Purkinje fibres emphasized the importance of the concentration of the element Ishihara and Pick reported an increase in rate of the automatic rhythm whereas according to Goldenberg and Rothberger large doses of calcium invariably inhibited automatic rhythms In the isolated mammalian left auricle addition of 1–3 cc of a 5 per-cent solution of calcium chloride to the Soejima solution abolished spontaneous contractions (Rothberger and Sachs)

Focal application of calcium chloride to the epicardium of the dog s heart only occasionally caused isolated ectopic beats this is in marked contrast to the profound effect of sodium or barium (*q v*) (Piccione and Scherf)

It was believed by some (Loewi McGuigan and Higgins) that calcium potentiates the effect of digitalis but this view was not substantiated by the investigations of Smith Winkler and Hoff Addarii and de Marchi found in isolated Purkinje fibres that calcium re established automatic rhythms which had been abolished by strophanthin

Clinical Observations

The experimental findings that calcium may abolish as well as elicit ectopic arrhythmias and even inhibit normal stimulus formation is duplicated by clinical observations in which calcium salts were given intravenously Dangerous disturbances of cardiac activity were observed in some cases while in others extrasystoles could be abolished in this way

Thus in some cases intravenous injections of calcium chloride abolished extrasystoles and paroxysmal tachycardias (Petzetakis Wolffe and Bellet Clarke) while the same dosage precipitated such arrhythmias in others Berliner who used 10 cc of a 20 per cent solution of calcium gluconate in twenty six patients who had not received digitalis previously saw ventricular extrasystoles appear in two patients Following intravenous administration of 40 grains of calcium chloride in a 2 per-cent solution Clarke observed ectopic beats and ventricular tachycardias in a patient without any evidence of heart disease and without premedication with digitalis Concerning the effect on normal impulse formation Berliner found sinus bradycardia in 67 per cent of his series of twenty six patients and sinus arrest in two instances Even after intravenous injection of only 4 cc of a 10 per-cent solution of calcium chloride sinus arrest was observed in a patient who had not received digitalis (Lloyd)

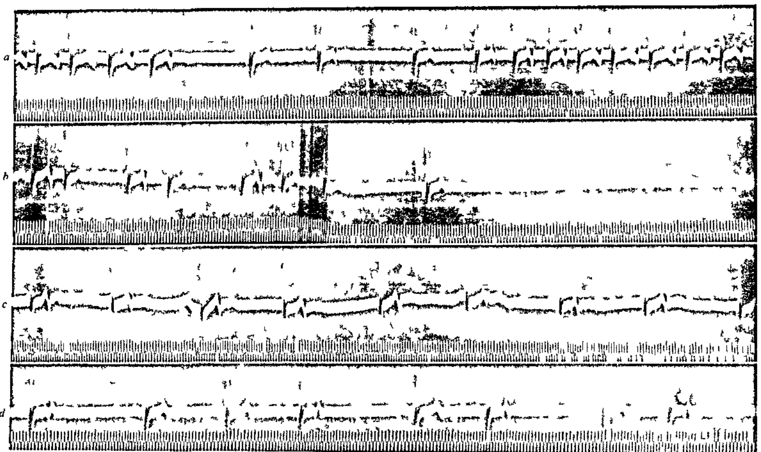


Fig 175.—All records lead 2 Before and after the intravenous injection of 10 cc of a 10 per cent solution of calcium chloride
For explanation see text

Two instances of death following the intravenous injection of calcium have been reported by Bower and Mengle in patients who had been given digitalis previously One of these was a thirty two year old woman without organic heart disease who had received 15 cc of digalen within six days Two minutes after the intravenous injection of 10 cc of a 10 per cent solution of calcium gluconate no heart sounds were heard and the patient died The other patient was a fifty five year old man admitted for a fracture of the femur Eight and one half cc of digalen had been given within twenty hours and the subsequent injection of 10 cc of a 10 per cent solution of calcium gluconate caused death within two minutes According to Bower and Mengle the effect upon impulse formation of calcium gluconate resembles that of calcium chloride

Such observations demonstrate that the intravenous use of calcium even in patients without organic heart disease is by no means free from risk This applies equally to cases with or without prior or simultaneous administration of digitalis

That even in subjects without evidence of structural heart disease the intravenous administration of calcium may be followed by most unpleasant reactions is illustrated by observations on a twenty three year old man who otherwise healthy suffered from numerous short attacks of auricular paroxysmal tachycardia which were separated by a few beats of normal sinus rhythm that is Extrasystolie a paroxysmes tachycardiques (*q v*) The frightening sequence of events which followed an intravenous injection of 10 cc of a 10-per cent solution of calcium chloride is illustrated in Fig 175

Fig 175a recorded before the injection shows the end of one and the beginning of another of such attacks The ectopic beats have peaked inverted P waves Fig 175b obtained about forty seconds after the injection shows auricular bigeminy with gradually lengthening P R intervals of the extrasystoles from 0 22 to 0 36 second followed by complete cardiac standstill lasting for more than one and a half minutes which was associated with loss of consciousness Following several blows to the precordium cardiac contractions started again At first the rhythm (*see* Fig 175c) was a slow A V rhythm either with preceding activation of the ventricles and disturbances of intra auricular conduction as manifested by the differences in shape of the P waves or with blocked auricular extrasystoles Subsequently (*see* Fig 175d) a slow sinus rhythm re established itself with blocked auricular extrasystoles having a shape different from those reproduced in Fig 175a Fortunately the patient recovered completely from this dangerous and frightening incident

SUMMARY

Experimental as well as clinical observations have shown that calcium salts may precipitate as well as abolish ectopic arrhythmias The kind of action seems to depend on the *species studied on the dose employed and on the simultaneous administration or otherwise* of other drugs The intravenous use of calcium salts is not free from risk irrespective of whether they are given alone or in conjunction with digitalis A potentiating action of calcium regarding digitalis cannot be considered as established

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BARIUM AND STRONTIUM

Barium

While in clinical practice the importance of absorbed barium salts is confined to the occasional—and fortunately rare—cases of accidental intoxication by soluble barium salts they have played a conspicuous role in the physiological studies of ectopic cardiac arrhyth mias

Experimental

In an extensive series of investigations already referred to in the chapter on the Ner vous System Rothberger and Winterberg first employed in 1911 barium in the form of its chloride to study electrocardiographically the arrhythmias occurring in the dog s heart *in situ* These authors found that ectopic beats originating in a ventricle as a result of the simultaneous faradic stimulation of the (preferably right) vagus and sympathetic nerves occurred more readily if the animal had previously been given small doses of barium chloride (0 005–0 01 gramme) intravenously With larger doses (0 025–0 05 gramme) such arrhythmias were observed after stimulation of the left accelerans without simultaneous vagal stimulation Still larger doses (0 05–0 1 gramme) precipitated ectopic arrhythmias without any stimulation of cardiac nerves A similar sensitizing action of barium was observed regarding epinephrine (*q v*)

These effects of barium namely either to predispose the heart in certain experimental conditions to develop or actually to cause ectopic arrhythmias have subsequently been

confirmed and studied in various ways In experiments on the perfused heart of dogs in which complete A V block had been produced Egmond found this element to cause ventricular ectopic beats and tachycardias Also in experiments on dogs Scherf (1926 1927) demonstrated that after injection of such small doses of barium that the electrocardiogram remained unchanged mechanical or electrical stimulation of a ventricle caused series of ectopic beats and local thermal stimulation by means of a thermode ventricular tachycardia such arrhythmias originating at the site of stimulation

Ventricular tachycardias elicited by large doses of barium can be abolished by the inhalation of a mixture of 20 per cent CO and 80 per cent O_2 whereas quinidine terminated such arrhythmias in only four out of ten experiments (Friedberg and Levinson)

The stimulating effect of barium upon impulse formation was also found in isolated Purkinje fibres of the dog s heart (Ishihara and Pick) and various types of arrhythmias sometimes resembling bigeminal rhythm were observed by Wachstein on strands of Purkinje fibres On isolated muscle bundles of the frog s heart barium chloride constantly initiated automatic activity the threshold concentration being 0 3 $\times 10^{-7}$ mol /ml (Deutsch and Lundin)

An important feature of the ectopic arrhythmias caused by barium which were encountered in the investigations discussed so far is that the ectopic beats showed varying shapes in the electrocardiogram and were not accurately coupled to the preceding beat If three or more ectopic beats occurred in succession they did so in an irregular sequence In dogs extrasystoles with accurate coupling so frequently observed in clinical practice could not be precipitated with any constancy by the systemic administration of barium salts In rabbits on the other hand anaesthetized with morphia and sensitized with small doses of barium Schott observed long series of bigeminal rhythm due to ventricular extrasystoles with accurate coupling as a result of clamping both carotid arteries (*see* chapter on Nervous System)

In dogs such arrhythmias could be elicited by the *focal* application of barium chloride (Piccione and Scherf) This was achieved either by brushing a 2–5 per-cent solution on a small area (2–3 mm diameter) of the epicardium or by the sub epicardial injection of 0 05–0 1 cc of a 1 per cent solution In this way bigeminal rhythm with constant coupling of the extrasystoles trigeminy and various other ectopic arrhythmias could be precipitated Figs 176 and 177 illustrate some of them

The tracing reproduced in Fig 176a was recorded after a 1 per cent solution of barium chloride was brushed on a small area of the conus of the right ventricle Extrasystoles originating at the site of application of the salt were observed after a latent period of six minutes The figure shows bigeminal rhythm one ventricular extrasystole occurring after each sinus beat The length of the coupling alternates between 0 44 and 0 46 second As every second extrasystole occurred very late in diastole at a time when most of the P wave of the next sinus beat was already inscribed these late extrasystoles show in the record the shape of combination beats (namely a combination between the undistorted shape of the extrasystoles as exemplified in the complexes of the series of the earlier extrasystoles and that of the sinus beats) the ventricles being activated at such times partly by the ectopic and partly by the sinus impulse

In the experiment from which Fig 176b was obtained 0 05 cc of a 1 per-cent solution of barium chloride had been injected sub-epicardially near the apex of the left ventricle After an interval of eleven minutes series of five to six extrasystoles in succession were recorded after each sinus beat the first extrasystole of each series showing constant coupling and the rhythm of the short paroxysms being fairly regular Such arrhythmias were usually transient and rarely lasted more than one minute At other occasions ventricular tachycardia with irregular rhythm was observed (Fig 177)

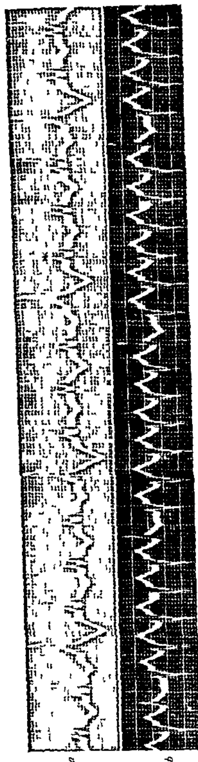


Fig 176.—From two different experiments on dogs *a* Extrasystoles originating from the site of application of a 1 per cent solution of barium chloride to the conus of the right ventricle *b* Extrasystoles precipitated by the sub epicardial injection of 0 05 cc of a 1 per cent solution of barium chloride near the apex of the left ventricle For further explanation see text

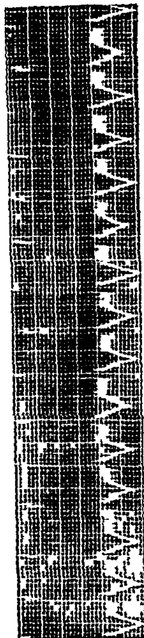


Fig 177.—From an experiment on a dog Ventricular tachycardia precipitated by the topical application of barium chloride

It is remarkable that ventricular tachycardias caused by barium salts whether administered intravenously or applied topically always showed such irregularities in the ectopic beats and often also different shapes of the ventricular complexes The significance of a sharp distinction between ectopic beats with accurate coupling (and constant shape) in the electrocardiogram and those with varying coupling (and varying shapes) is discussed in the chapter on Mechanism

Clinical Observations

Cases of poisoning by soluble barium salts are on record in which irregular heart action was observed which can be attributed to ectopic arrhythmias Such incidents have been reported in connexion with radiological investigations (Krause and Kading Hirvonen) or due to contamination of flour with barium carbonate intended as rat poison (Morton)

Because of the narrow margin between therapeutic and toxic doses the use of barium chloride recommended in doses of 20–30 mgm three to four times a day by Cohn and Levine for the treatment of Stokes Adams attacks in complete A V block with slow ventricular rate should be discouraged Untoward effects have been described by McMillan and Wolferth and by Mahaim Ephedrine is far preferable in such cases On no account should epinephrine be given in combination with barium

Strontium

On isolated muscle fibres of the frog s heart Deutsch and Lundin found that addition of strontium salts to the nutrient solution increased the automaticity in a way similar to barium but in order to produce a threshold effect fifty times as much strontium was required

In experiments on dogs the intravenous injection of 10–15 cc of a 10-per-cent solution of strontium chloride did not cause ectopic beats (Rothberger and Winterberg) These authors considered the possibility that larger doses may have a similar effect as barium salts since previous experiments on cats had shown that several cc of a 20 per cent solution of strontium caused arrhythmias (no electrocardiograms were taken)

SUMMARY

In experimental work barium chloride has played an important part in the investigation of ectopic arrhythmias Its systemic application either alone in larger doses or in smaller doses combined with other experimental interferences precipitates with rare exceptions ectopic beats with varying coupling and varying shapes in the electrocardiogram or ectopic ventricular tachycardias Topical application of this compound to the exposed surface of the heart on the other hand elicits extrasystolic arrhythmias with constant coupling of the extrasystoles apart from various other ectopic arrhythmias The relevant literature on these investigations is reviewed and some aspects are illustrated by personal observations The clinical use of barium chloride in the treatment of Stokes Adams attacks in complete A V block is discouraged

Brief reference is made to the very scanty literature on the effect of strontium salts regarding ectopic arrhythmias

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MAGNESIUM

The general effect of the magnesium ion on the heart is that of a cardiac depressant for a short review of the relevant literature *see* Kisch (p 750)

Experimental

In early studies on ectopic arrhythmias it was noted that magnesium salts failed to have any stimulating effect on ectopic impulse formation (Rothberger and Winterberg Abder halden and Gellhorn) The effect upon such arrhythmias of magnesium salts did not attract much interest when it was found that their intravenous administration abolished arrhythmias which occurred in cattle as a result of calcium injections given for the treatment of milk fever and grass tetany (Seekles Sjollema and van der Kaay)

The use of magnesium salts in the treatment of ectopic arrhythmias in man is largely based on the report of Zwillinger in 1935 who found that magnesium sulphate abolished in man ventricular extrasystoles produced by digitalis Subsequently Rothberger and Zwil linger observed in dogs that it suppressed ectopic beats elicited by barium or strophanthin A similar though transient effect of magnesium salts given intravenously was established by Hueber and Lehr in rabbits dogs and cats regarding arrhythmias produced by aconitine these authors recommend the use of magnesium gluconate as it results in a smaller drop in blood pressure than other magnesium salts Szekely and Wynne produced ectopic ventri cular arrhythmias in cats by means of digitalis and strophanthin and found that magnesium sulphate (0 5–3 5 cc of a 20 per cent solution given intravenously) abolished ventricular extrasystoles in all four instances of bigeminy and restored sinus rhythm in three out of eight instances of ventricular tachycardia

More recently Pines Sanabria and Arriens observed in dogs a protective action of magnesium sulphate against ventricular fibrillation resulting from mercurial diuretics and recommended the incorporation of small quantities of this salt (0 5 cc of a 20 per cent solution) into the solution of the mercurial diuretic (While this observation is of con siderable physiological and pharmacological interest we should like to emphasize that in our opinion clinically mercurial diuretics should only be given intramuscularly)

Like so many compounds magnesium salts may in certain circumstances have the oppo site effect namely precipitate ectopic arrhythmias (Smith Winkler and Hoff 1939 Miller and van Dellen)

Clinical Observations

As already mentioned in 1935 Zwillinger recommended the intravenous administration of magnesium sulphate for the treatment of extrasystoles and paroxysmal auricular tachycardia Ten to twenty cc of a 15 per-cent solution or 10 cc of a 30 per cent solution were found to abolish digitalis extrasystoles (Zwillinger Bloch and Pick) On the basis of experimental observations Smith Winkler and Hoff (1939 1942) expressed doubts whether the salt in the recommended doses could have much effect on cardiac rhythm but Boyd and Scherf confirmed the efficacy in terminating attacks of paroxysmal auricular tachycardia in eight instances the slow intravenous injection of 15–20 cc of a 20 per cent solution stopped the attack in every case within a few seconds without any untoward effect Favourable results in paroxysmal auricular tachycardia were also reported by Szekely and in ventricular ectopic rhythms due to digitalis by Szekely and Wynne In ectopic arrhythmias caused by digitalis injections of magnesium may be life saving but should not be repeated at short intervals because of the depressant effect of the salt upon the myocardium

In clinical observations too the opposite effect of magnesium sulphate was occasionally found (Boyd and Scherf) Sometimes in cases of paroxysmal tachycardia ventricular extrasystoles temporarily occurred immediately after the injection In patients with ventricular extrasystoles a transient increase in their frequency and sites of origin was often observed (Enselberg *et al*) Such clinical findings accord well with similar experimental ones referred to above

SUMMARY

The rather scanty literature on experimental work on the effect of magnesium salts on ectopic arrhythmias is reviewed Regarding the clinical application it is concluded that the intravenous administration of magnesium sulphate has a place in the treatment of paroxysmal auricular tachycardia

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MERCURIAL COMPOUNDS

Experimental

In experimental work organic mercurial compounds have been found to produce ventricular premature beats ventricular tachycardia and finally ventricular fibrillation (Salant Jackson McCrea and Meek Barker *et al*) The doses employed in such investigations were however considerably higher than those given in clinical practice According to Pines Sanabria and Arriens this action of mercurial compounds can be prevented by magnesium sulphate (*q v*)

Clinical Observations

With the introduction of mercurial diuretics into clinical practice the effect upon cardiac rhythm of such compounds became of great clinical importance That the intravenous injection of a mercurial diuretic may quickly be followed by sudden death has been known since Redlich s observation in 1925 concerning Novasurol More recently such fatal accidents have been reported on several occasions and while in some cases they may have been due to an allergic reaction of the patient in others ectopic arrhythmias were responsible Ventricular extrasystoles and ventricular tachycardia were observed by Chastain and Mackie Volini Levitt and Martin Ben Asher In a recent investigation by Wolff and Sagall the electrocardiographic changes were studied which occurred in 137 patients as the result of 319 injections of mercurial diuretics In thirty six instances extrasystoles occurred the majority of which were ventricular in origin one patient developed ventricular paroxysmal tachycardia

Occasional premature contractions were found in three out of a hundred patients who had received injections of Thiomerin a more recent mercurial diuretic (Herrmann *et al*)

Since the rate of absorption of the mercurial compound seems to be an important factor in precipitating or otherwise ectopic arrhythmias such preparations should exclusively be given intramuscularly and their intravenous use should be discouraged

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MISCELLANEOUS DRUGS

This section is devoted to brief notes on some compounds which have or may acquire some experimental or clinical interest in connexion with ectopic arrhythmias but which do not warrant a more detailed discussion

Ergotamine With the recent discovery of the di hydrated alkaloids of ergot their effect on ectopic arrhythmias was studied This seemed promising in view of the part played by the sympathetic in the precipitation of such arrhythmias and the sympatholytic effect of ergot alkaloids generally These comparatively recent studies are at present still very much in the beginning

Bennett Dhuner and Orth found in dogs and monkeys that dihydro ergocornine (DHO 180) seemed more effective than dihydro ergotamine (DHE 45) in preventing ectopic arrhythmias induced by cyclopropane and epinephrine A clinical trial of such compounds on twenty three patients was far from conclusive

Rothlin and Cerletti reported that in dogs the pre fibrillary ectopic arrhythmias due to chloroform adrenaline could mostly be prevented by the intravenous injection of Hydergin (0 1 mgm per kilo on an average) Hydergin consists of equal parts of the three alkaloids dihydroergocornine dihydroergocristine and dihydroergokryptine and is also known as CCK 179 Further studies by these workers are announced about the extent of such protection against arrhythmias produced in various ways and about the mode of action of such protection

Methyl fluoroacetate, which was introduced as a rodenticide caused ventricular fibrillation in monkeys rabbits goats and horses but not in dogs and guinea pigs (Chenoweth and Gilman) These studies emphasize the pronounced differences in the reaction to this compound of various species

Emetine has been reported to cause ectopic beats both experimentally (Boyd and Scherf) and clinically (Baer Hardgrove and Smith Klatskin and Friedman) In clinical practice ectopic arrhythmias play only a very small part compared with other electrocardiographic and toxic manifestations of this compound

During intravenous administration of **histamine** to twenty five patients ventricular extrasystoles were seen in four instances when the injection was given rather quickly (Peters and Horton)

Ventricular extrasystoles were also observed as a result of the administration of **low fatty acids** (Hall and Waldman)

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CHAPTER IX

SOME MAINLY PHYSIOLOGICAL ASPECTS OF EXTRASYSTOLES AND OF ECTOPIC BEATS GENERALLY

DYNAMICS OF CONTRACTION AND REFRACTORY PERIOD OF EXTRASYSTOLES AND POST EXTRASYSTOLIC BEATS

Extrasystoles and Ectopic Beats Generally

The force of an artificially induced cardiac contraction is independent of the intensity of the stimulus the all or none law Bowditch s description in 1871 of his fundamental discovery of this law in the apex of the frog s heart is of such admirable lucidity that it deserves to be quoted

An induction current of the smallest intensity which yields a cardiac contraction does not produce the smallest possible contraction nor does the force of the latter increase to a maximum if the intensity of the stimulating current increases In our preparation the induction current either yields a contraction or fails to do so if the former it produces at once the greatest possible contraction which it was capable to elicit at the given moment It follows that variations in strength of contractions of the cardiac apex are due to variations in the condition of its muscular fibres It seems hardly necessary to emphasize the great practical importance of this sentence (P 174 our translation)

This law was found to be valid for the mammalian heart by McWilliam (1888) and is now universally accepted It is true that some apparent exceptions were reported namely that a stronger stimulus yielded a stronger contraction these were found in hearts poisoned with chloral hydrate (Rohde) or alcohol (Rossler) and in the dying heart It was shown however by Bornstein (1906b) and by Koch that such observations can be reconciled with the all or none law if the velocity of conduction of the impulse is taken into consideration A stronger stimulus directly affects a greater number of fibres In normal conditions the velocity of conduction is so great that the number of fibres directly stimulated is immaterial as far as the resulting force of contraction is concerned In hypodynamic hearts on the other hand conduction may be retarded to such an extent that considerable differences in the period of latency and in speed of contraction exist between the various areas so that a direct stimulation of a larger number of fibres produces a stronger contraction

Kleinknecht showed manometrically on the hearts *in situ* of frogs cooled to a rectal temperature of -3 C that extracontractions precipitated by induction shocks just before the next normal contraction was due (that is very late in diastole) yielded higher intra ventricular pressures than normal beats and that a stronger stimulus produced a greater increase in pressure even if it occurred a little earlier in diastole and thus at a moment when recovery was less complete He explained this apparent exception from the all or none law by the as umption that owing to the pronounced cooling conduction of the impulse of normal beats was slowed and thereby lead to a smaller increase in intra ventricular pressure than that produced by the artificial beats in which many fibres were simultaneously stimulated Again the reduced velocity of conduction is held to account for the apparent anomalies

The all or none law does not mean that the force of contraction of artificially produced

beats is constant for any given preparation On the contrary Bowditch in his paper of 1871 already quoted pointed out that Cardiac muscle possesses the notable property that its susceptibility for stimuli is altered by the contractions which it has performed that is to say after a longer series of contractions a weaker stimulus very often is effective in producing a regular sequence of pulses than had been the case before (P 151 our translation) Bowditch also found that if the apex of the frog s heart is stimulated after a longer interval the contractions increase in height at first steeply and subsequently more gradually until a maximum is reached Woodworth confirmed this observation of the staircase phenomenon for the mammalian heart (spontaneously beating apex of the dog s heart) It is due to a temporary increase by the contraction of the contractility of the heart in the event of a subsequent stimulation provided the stimuli follow one another at sufficiently short intervals and is probably related to or a manifestation of the supernormal phase of recovery (*see* chapter on Mechanism) During the interval after a contraction the heart regains its excitability being refractory during most of systole The length of the optimum interval between two successive stimuli for yielding maximum contractions depends on two opposite forces the stimulating effect of a rapid succession of contractions and the recuperative effect of a long pause Woodworth showed that in this respect a difference exists between the frog s and the dog s heart in the former the optimum interval between two successive stimuli is four to five seconds whereas in the latter it is about one second He demonstrated that the strongest possible contraction occurred if two or more contractions were elicited in rapid succession and then the apex was stimulated after a considerable interval conversely the smallest contractions were observed if the apex was at first stimulated at a slower rate and the last of such stimuli was followed by one at the briefest possible interval While Woodworth attributed these observations to the effect upon contractility of contractions following one another in rapid or slow succession the emphasis to day is more on the supernormal phase of recovery and the varying duration of the refractory period as the main factors

The refractory period is one of the important factors which by affecting the condition of the heart muscle at the moment of a subsequent contraction determine the strength of extra-contractions The fact that during most of systole the heart muscle is in an absolute refractory period which is followed by a stage of gradually increasing excitability termed relative refractory period is too well known to merit any detailed discussion In general the extracontraction will therefore be the weaker the earlier in diastole it occurs This has been established in various species namely in the frog by Marey (1876) aortic bulbus of the frog s heart (Engelmann 1882) sinus of the frog s heart (Tigerstedt and Stromberg 1888) and in the mammalian heart (Gley 1889 Cushny and Matthews 1897 Hirschfelder and Eyster 1907) (for references *see* Tigerstedt 1921 Vol 2 p 35) Conversely within certain limits an extracontraction can be elicited the earlier in diastole the stronger the extra stimulus is—which is only another way of describing the relative refractory phase

A similar curve of the recovery of excitability is obtained if the duration of extrastimuli of constant intensity is varied Using condenser discharges as test stimuli von Werz established that the longer the interval after the preceding excitation the shorter a test stimulus can be to elicit a contraction

The refractory phase decreases with increasing rates and that of an extrasystole is shorter than that of normal beats

The change in the duration of the refractory phase with change of rate explains an observation first made by Trendelenburg (1903) If a frog s heart is rhythmically stimulated with gradually increasing rates the ventricle will respond to each stimulus up to a rate which if given abruptly would have produced half rhythm (that is the ventricle contracting only in response to every other stimulus) On the other hand if with a high rate of stimulation half rhythm was present and the rate of stimulation was then gradually decreased whole

rhythm did not occur at a rate at which it had formerly been present but only with a lower rate of stimulation The refractory phase accounts for these phenomena with a gradually increasing rate the refractory period gradually becomes shorter so that successive beats tend to fall just outside the non responsive phase but if the rate is abruptly increased the first impulse of the rapid sequence falls within the refractory period of the preceding beat which is long owing to the former slow rate and thus is ineffective the next impulse yields a response but owing to the long preceding interval the refractory period of this beat too is long and a 2 1 response thus becomes established Similar considerations hold good for the observations made with gradually decreasing rates of stimulation

Mines confirmed and amplified these observations He showed that by this method the length of the refractory period can be determined and also demonstrated that the tran sition from half to whole rhythm during rhythmic artificial stimulation can be brought about by interpolating an extra stimulus at the proper time An extra stimulus applied shortly after the stimulus to which response is missing may provoke an extrasystole The extrasystole will of course have a refractory phase shorter than the refractory phase of the preceding beats and although the next of the rhythmic series of excitations will fall within it the next but one (belonging to the hitherto unaccented series) will find the tissue ready to respond But it will also reach the ventricle sooner after a response than had an effective stimulus before thus the refractory phase will be shorter again and probably so short that the next stimulus falls outside the refractory phase Once started the new rhythm continues The nature of the mechanism by which one single extrasystole may under certain circumstances produce enduring effects on the heart rhythm is thus quite evident (p 365/6) Similar conditions have been demonstrated in the frog s heart poisoned with veratrine in which a 2 1 block was present (de Boer 1915 1916) and a similar mechanism was sug gested by Scherf in order to explain the prolonged conduction in the ventricles of the second beat in clinical cases of dropped beats (Wenckebach periods) and of the difference in shape of the first of a series of extrasystoles

The observation that the refractory phase of an extrasystole is shorter than that of nor mal beats was first reported by Trendelenburg in 1903 and has repeatedly been confirmed (de Boer 1915 Umrath Lewis and Master Schellong and Schutz Buchthal Andrus and Padget Eccles and Hoff)

Schellong and Schutz investigated on heart muscle strips the relationship between refractory phase and monophasic action current the duration of the latter could be con sidered to equal the duration of the state of excitation and to correspond closely to the duration of the absolute refractory phase (Adrian 1921 Drury and Brow) The response to a test stimulus applied as induction shock at various times and with various intensities after a preceding main (conditioning) stimulus was studied in such a way that the exploring electrode for leading off the monophasic action current was at the same time used as the cathode of the stimulating electrodes applying the test stimulus this arrangement made it possible to investigate the refractory period of the very site from which the action current was recorded The length of the absolute refractory period was examined by deter mining the shortest interval after an excitation at which a test stimulus yielded an action current The relative refractory period was measured as the smallest interval between two contractions for the second one to have an action current of the same duration as that of the preceding one This was investigated both for excitations following maximal contraction and those following an extrasystole in the latter event three stimuli were used and the action current of the third contraction was compared with that of each of the two preceding beats Schellong and Schutz found that the end of the absolute refractory period coincided with the end of the monophasic action current (that is with the end of the state of excitation) An extrasystole was found to have a shorter action current and therefore a shorter absolute refractory period Comparative measurements of the relative refractory period of an

excitation following one with a normal and one with a shortened duration of the mono phasic action current respectively revealed that in these two instances the duration of the relative refractory period was the same This means that the shortening of the total refrac tory phase of an extrasystole is solely due to that of the absolute refractory phase while the relative refractory period has the same duration in normal and in extrasystolic beats Similar conditions were found after a series of forced contractions in short succession (Pohl) and were also encountered in the auricle of the frog s heart (Buchthal)

The above conditions were established for contractions produced by induction shocks For excitations elicited by rectilinear electrical impulses the results were different in 92 per cent of the observations threshold stimuli were effective at the end of the monophasic action current With this kind of stimulation full excitability is regained very quickly and the end of the relative refractory period coincided approximately with the end of the mono phasic action current If contraction curves are recorded this means that an extrasystole can be produced by a threshold stimulus shortly after the summit of the preceding systole (Schutz and Lueken)

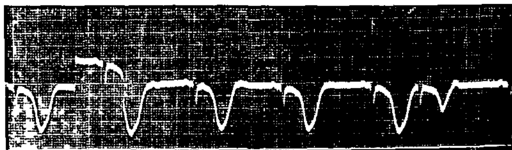


FIG 178 —The Q T interval of the extrasystole (penultimate beat) measures 0 60 sec as compared with the 0 68 sec of the sinus beats

In clinical electrocardiography the length of the refractory period can approximately be determined by the duration of electrical systole that is by the length of the Q T interval In Fig 178 the Q T interval of the extrasystole measures 0 60 second as compared with the 0 68 second of the sinus beats (which abnormally long interval was due to myocardial damage)

Reports in the literature about the length of the Q T interval of extrasystoles are con flicting (*Fridericia Miki White and Mudd Calandre and Rico*) *Most investigators con* sidered the Q T interval in relation to the preceding shortened interval that is the coupling of the extrasystole The lack of uniformity of the reported results is not surprising for various factors operate in different directions in determining the Q T duration of extra systoles the increased width of the ventricular complexes is apt to increase it whereas the shortened preceding interval tends to have the opposite effect A more recent investigation by Berliner draws attention to the fact that the QRS and the RS T intervals of auricular extrasystoles vary independently the RS T intervals were found to be usually shorter than those of the normal beats though exceptions were observed the greatest degree of shorten ing occurred in extrasystoles with marked widening of the QRS complexes so that the total Q T intervals of such beats were not longer than those of normal ones Similar discrepan cies exist in regard to the Q T interval of the first post extrasystolic beat with the added source of confusion that the reverse interpretation of figures was given according to whether the length of the Q T interval was considered in relation to the long preceding compensatory

pause or to the interval between normal beats (Hegglin and Holzmann Schlomka and Konigslow Marx) It seems to us that the disappointing result of such determinations is only to be expected since with abrupt change of rate the Q T interval adapts itself to the new rate only gradually and in the course of several beats (4–10 Lepeschkin 5–30 in the frog Blair Wedd and Young) Taking this observation in conjunction with the various other complicating factors detailed above such investigations seem rather futile

Owing to the fact that cardiac muscle has an absolute refractory period which is long as compared with that of skeletal muscle superposition of contractions does not usually occur and extracontractions are as a rule not stronger than normal beats Observations of superposition of extracontractions have been reported in hearts which for various reasons were in a hypodynamic condition or under the influence of poisons A few examples may be mentioned Frank (1899) reported superposition in the frog s heart if sinus and vagus were simultaneously stimulated and intraventricular pressure was low the same phenomenon was found also in the frog s heart as an effect of certain poisons muscarine (Walther Rhodius and Straub) chloral (Rohde Schultz Bornstein 1906a) potassium chloride (Burridge) also cooling (Frey) Most of these authors also Junkmann considered a shortening of the refractory period to be the underlying factor This view was contested by Mangold and Shimizu who by means of a pure NaCl solution without K or Ca obtained superposition of extracontractions in the frog s heart in a high proportion of experiments (59 out of 132) They assumed that the damaged heart was only capable of partial contractions and that the superposition of extracontractions was due to the additional contraction of fibres which had not taken part in the preceding beat These authors did not therefore consider superposition as a true summation A similar view was held by Mononobe but his experiments interpreted to show that there was no constant relationship between the length of the refractory phase and the occurrence of superposition are open to doubts on technical grounds

Some light was thrown on this problem by Bertha and Schutz and by Schutz By comparison with normal hearts the damaged one has a shorter action current and this was invariably the case in all instances of superposition of extrasystoles that is to say in those precipitated by induction shocks as well as in the rarer instances of spontaneous superposition In all such cases two successive monophasic action currents were recorded each of reduced duration and amplitude Whatever the mechanism underlying superposition may be—and this remained unsolved—from an electrical point of view the phenomenon consists of two separate events following one another in close succession mechanically superposition constitutes a special manifestation of the action of a damaged heart

Rihl (1907) found in the mammalian heart perfused by Langendorff s method and being in a poor state of nutrition that an extracontraction can yield a higher contraction (1) by superposition and (2) by being higher in itself without superposition The first variety was observed mainly with very premature extracontractions the latter with less premature ones Rihl considered the possibility that the ventricle has a higher contractility in an earlier phase of the excitable period than in a later one (dass die Kammer in einem fruheren Stadium der erregbaren Phase eine grossere Contractilitat besitzt als in einem spateren p 262) This remark deserves mentioning since it anticipates by several years the report of the presence of a supernormal phase of recovery by Adrian and Keith Lucas (1912) But Rihl s observations were contested on technical grounds by Wiggers (*see* below)

With the heart *in situ* or in the heart lung preparation once the stage of ventricular filling has started the force of a premature contraction depends largely on the initial length of the muscular fibres and thus on the degree of filling It is this factor which is of the greatest importance clinically and in many respects physiologically but it is not the only one

According to Straub extrasystoles cause a diminished systolic power of the systolic contraction of the ventricles and a diminished output Furthermore with the heart *in situ* not only is the degree of ventricular filling smaller the earlier in diastole the extrasystole occurs but also the pressure in the aorta is the higher which such extrasystolic contraction has to overcome (Wenckebach and Winterberg)

The most comprehensive and convincing investigation of the force of beats elicited by artificial stimulation is the one by Wiggers (1925) In experiments on dogs he optically recorded the pressures in the left ventricle and in the aorta in certain experiments also in the right ventricle or in an auricle Stimuli were applied by means of induction shocks to the left ventricle in different phases of normal beats or during artificial rhythm forced upon the heart during vagal standstill Wiggers found that compared with normal beats the premature contraction had a prolonged isometric contraction phase a slower gradient of rise of pressure and a shorter ejection phase resulting in a *shortening* of total systole From this it could be concluded that the smaller systolic discharge of premature beats was not solely due to the smaller pressure developed within the ventricle but in part attributable to the reduced phase of systolic ejection Since the degree of diastolic filling and the initial tension modify not only the volume of systolic discharge but also the duration of the ejection phase Wiggers eliminated the first of these two factors by comparing normal and ectopic beats under conditions where initial pressures and diastolic fillings were the same This was achieved by comparing a series of normal beats with a series of contractions artificially produced at the same rate (during vagal standstill) The result was that with the latter rhythm intra ventricular pressures still remained lower and systolic discharges smaller but total systole was *lengthened* the phase of isometric contraction as well as that of ejection partaking This indicated that the altered dynamics of ectopic beats were partly due to peculiarities in the nature of the muscular contraction According to Wiggers these are due to an abnormal spread of the artificial contraction having the result that the muscular *fractions are excited in an abnormal order or some of them not excited at all* This conception was largely based on Lewis and Rothschild s work on the spread of normal and artificial ectopic beats Regarding the latter these authors assumed the impulse to spread slowly through ordinary muscle until it reached the Purkinje network through which conduction to the contralateral and most of the remaining part of the ipsilateral ventricle was fast and occurred in the normal order (*see* section on Spread of the Excitation of Ectopic Beats pp 371–373) Wiggers further results regarding the intraventricular pressure curves seemed to find a plausible explanation by these views Thus if a stimulus was applied to one ventricle and intraventricular pressures were recorded simultaneously from the two ventricles the strength of the beat of the contralateral ventricle (that is the one not stimulated) was proportionately greater than that of the stimulated one and the gradient of pressure elevation was *much steeper in the non stimulated one* These differences were explained by the fact that the ventricle which had not been stimulated was activated through normal pathways and its contraction thus took place by the normal sequence of contraction of the individual fractions This view was supported by the observation that contractions elicited very late in diastole were never quite equal in height to normal ones in such instances it was assumed that owing to interference of the artificial and the normal stimulus *some muscular fractions escaped being activated or that an orderly mode of contractions may perhaps be necessary to produce a maximal effect*

Rothberger and Scherf on the other hand found in dogs a higher pressure in the left ventricle (optically recorded) in left ventricular tachycardia produced by direct stimulation of the left ventricle with condenser discharges as compared with the left intra ventricular pressure in right ventricular tachycardia elicited in the same way

Wiggers also re investigated the duration of the refractory period which with his method of optically recording intraventricular pressure changes he was able to do with a

greater degree of accuracy than had been possible by using mechanical records of movements during contraction He found that while during the phase of isometric contraction and during the early stage of the ejection phase the heart was refractory to all stimuli the absolute refractory period did not extend throughout the latter part of ventricular systole the length of this non refractory portion of ventricular systole covers on an average the last 0 06 second before the termination of systole No evidence of superposition of such contractions elicited during the latter portions of systole was found and reports of such superposition were attributed to faulty technique or to a grossly abnormal condition of the heart Wiggers gives reasons for the belief that the contraction resulting from such early stimuli is not due to excitation of fibres which are already relaxed but to disappearance of the state of refractoriness during the latter part of contraction

As far as a moderately strong brief D C shock is concerned which was applied considerably before the T wave of an electrogram recorded at or near the point of stimulation Moe Harris and Wiggers (1941) found that a stimulus of this kind and timing produced one response shortly after the T wave By analysing the latency of such stimuli applied at different moments in relation to the summit of the preceding T wave and by recording the polarizing current itself these authors presented evidence which indicated that the response to such early stimuli is probably not due to an actual systolic excitation but to the creation in the tissues of a decrementing polarization potential which is sufficient in duration and in intensity to excite early in the next relatively refractory phase

To return to Wiggers work on the dynamics of artificially induced contractions just after the isometric relaxation phase a small difference in the time of the premature contraction produced marked changes in the pressure maximum of the premature beat this is due to the influence of filling with the resultant increase in the length and tension of the muscular fibres

Regarding the factors which determine the effectiveness of premature contractions according to Wiggers effective premature contractions—that is those producing a rise in intraventricular pressure sufficiently high to eject blood into the aorta—are recognized

(1) by the production of a clear cut aortic pulse
(2) by the fact that the intraventricular pressure rises beyond the point where ejection normally takes place

and

(3) by the sharper drop in pressure during the isometric relaxation phase indicating that the contraction had not been of an isometric character

The fundamental factor which determines whether or not a premature contraction is effective is a minimal interval of ventricular filling on an average this was found to be 0 12 second between the end of systole and the onset of the premature contraction Since the interval between the beginning of diastole and the opening of the A V valves measures about 0 08 second a minimal interval of about 0 04 second is required for a degree of ventricular filling adequate to cause ejection against normal arterial diastolic pressure The actual length of this interval depends on the height of diastolic pressure and the rate of ventricular inflow

This effect of rate upon presence or absence of ejection is well shown in the study of Coblentz *et al* These authors catheterized adult patients with various cardias lesions and recorded intra ventricular and sometimes also pulmonary artery pressure curves and electrocardiogram In tracings of nine patients in which ventricular extrasystoles occurred at various phases of diastole the shortest coupling of the ectopic beat resulting in a (left or right) ventricular ejection varied between 0 340 second at 130 beats per minute and 0 640 second at 58 beats per minute this relationship was found to be linear (their Fig 11 on p 12)

Of the various points arising from Wiggers extensive studies we should like to emphasize

(1) once ventricular filling has started its degree largely determines the height of intraventricular pressure produced by the premature contraction
(2) in addition to (1) the mechanism of a premature contraction due to an ectopic impulse differs from that of normal beats in such a way that the pressure maximum of an ectopic beat tends to be lower than that of a normal beat originating in otherwise identical conditions
(3) in addition to (1) and (2) the smaller systolic discharge of a premature contraction is partly attributable to the shorter phase of systolic ejection of the premature beat

A more recent clinical observation is in accordance with Wiggers experimental findings By optically recording the pressure changes in the brachial artery in patients with auricular fibrillation Buchbinder and Sugarman showed that the duration of the preceding cycle length was the most important factor determining the degree of pressure changes if extrasystoles occurred in such cases they produced a rise in diastolic and fall in systolic pressure which were too great as to be explained solely by the short cycle length preceding the ectopic beat extrasystoles occurring not more prematurely than some of the conducted beats produced so small an increase in intra ventricular pressure that such contractions had no appreciable influence on the pulse curve that is failed to open the semilunar valves This seems to be an instructive confirmation of Wiggers views that the abnormal mechanism of the premature contraction is an important factor accounting for the reduced efficiency of such beats The fundamental mechanism seems to be the less perfect summation of fractionate contractions when the excitation waves spread from a ventricular focus and in part to a less efficient mechanical twist of the ventricular muscle scrolls when the septum is not excited first (Wiggers 1944) Differences between normal and ectopic beats in the rate and sequence of activation of the various portions of the heart can be expected to be of importance also from a different point of view H C Wiggers (1937) has shown that the impulse of normal beats reaches all parts (except one area) of the ventricles within about 0 005 second that is practically simultaneously (*see also* section on Spread of the Excitation of Ectopic Beats p 370) On the other hand Ashman and Hull calculated that it takes at least 0 035 or 0 04 second possibly more for an impulse to travel from the Purkinje network in a lateral ventricular wall to the bifurcation of the bundle and that conduction by way of the interventricular septum does not take less time than via the bundle branches and bifurcation It seems reasonable to assume that such great differences in the rate of activation of the various portions of the heart play an important part in accounting for the differences in the dynamics between normal and ectopic beats

Investigations in man about the length of the isometric contraction phase of extrasystoles seem on the whole to be in accordance with the experimental findings Blumberger and Blumberger and Meyer found that with rare exceptions extrasystoles particularly ventricular ones have a lengthened isometric contraction phase Their ejection phase was shortened The first post extrasystolic beat showed the reverse alterations in the lengths of these intervals

More recently Weissel and Vetter pointed out that it is an unjustifiable simplification to designate as Anspannungszeit * the interval between the beginning of electrical activation

* We do not find it possible to give an accurate translation of Anspannungszeit as employed by these authors The nearest would be isometric contraction phase but it is part of the object of their paper to draw attention to the mistake made in identifying two intervals namely that between the beginning of electrical activation of the ventricles and the opening of the semilunar valves on the one hand and that between the beginning of the steep rise of intra ventricular pressure and the opening of the semilunar valves on the other This confusion arises from the mistaken assumption that the moment of beginning electrical activation of the ventricles coincides with that of the beginning of the sharp rise in intra ventricular pressure

of the ventricles and the opening of the semilunar valves since there is a distinct interval between the beginning of electrical activation (beginning of the Q or R wave) and the beginning of the steep rise in intra ventricular pressure They termed this interval elektro-pressorische Latenz (electro pressor latent interval) In nine patients with congenital cardiac lesions in whom they recorded intracardiac pressure curves and electrocardiogram they found that extrasystoles had a shortened isometric contraction phase whereby the electro pressor latent interval as well as the isometric contraction phase in its purely mechanical sense partook Both these phases were found shortened in the first post extrasystolic beat Coblentz *et al* *on the other hand found the interval between* Q and the beginning of right ventricular systole (corresponding to Weissel and Vetter s electro pressor latent interval) of ventricular extrasystoles normal in nine cardiac patients

We consider it desirable to make a brief reference to this recent work as it illustrates the difficulties in determining these various phases of cardiac contraction in man and also supports our doubts about the applicability to clinical problems of Blumberger s work in its present stage (*see* below p 364) this author identifying the moment of beginning mechanical with that of electrical systole

The Post Extrasystolic Beats

The first post extrasystolic beat usually is stronger than the normal beats of the individual case This was first reported in the isolated heart of the frog by Langendorff in 1885 and considered by him to be a vagal effect *a view which he subsequently abandoned (see* below) The same was found to prevail in the mammalian heart by McWilliam and by Gley and studied in more detail by Langendorff (1895 and 1898) Langendorff found that *the smaller the extrasystole the larger the first post extrasystolic beat and* interpreted this observation as indicating a compensatory phenomenon effecting a constancy of work equal amounts of energy being developed during equal periods While this explanation proved untenable the observation was confirmed by various authors (for example on the bloodless amphibian heart by Bottazzi on the mammalian heart by Cushny and Matthews)

Woodworth investigated this phenomenon in more detail on the spontaneously beating apex of the dog s heart He found that the first post extrasystolic beat was stronger than the normal almost without exception its average height being 124 4 per cent of that of the normal beats The earlier the extrasystole the higher the first post extrasystolic beat tended to be and the degree of prematurity was more important than the length of the post extrasystolic interval *Even if the latter was not longer than the interval between normal* beats the post extrasystolic beat was stronger and this was attributed to a strengthening effect of the extracontraction Woodworth also found that two successive extracontractions tended to be followed by an exceptionally strong post extrasystolic beat *and that several* post extrasystolic contractions may show increased height In the frog s heart on the other hand the greater height of the post extrasystolic beat was found to be due to the preceding pause and no effect of the premature beat itself as was established in the dog s heart could be traced This difference between the two species was attributed to the slower rate of the *apex of the dog s heart as compared with that of the frog s ventricle*

Rihl (1906) confirming Woodworth s findings in the mammalian heart concluded that the greater height of the first post extrasystolic beat depended solely on the prematurity of the extrasystole and on the length of the post-extrasystolic interval the ectopic origin of the premature contraction was thought to be without importance since premature nomotopic beats had the same effect *Again in accordance with Woodworth Rihl found that the* prematurity of the extracontraction was the salient factor for a higher first post-extrasystolic contraction was observed also after an interpolated extrasystole an observation later confirmed by Busquet and Tiffeneau Bornstein s (1906c) objection that the coronary circulation

was the underlying factor accounting for Rihl s observation is unacceptable because of Woodworth s results on the isolated apex Moreover as early as 1888 McWilliam had observed the phenomenon in the mammalian heart when superior and inferior vena cava were clamped and the ventricular cavities were no longer distended with blood

Regarding the height of the subsequent post extrasystolic beats conflicting findings were published Rihl found that in some experiments they were of increased in others of reduced height An increased amplitude of the second post extrasystolic beat was reported by Busquet and Tiffeneau A gradual increase in the height of several post extrasystolic beats reminiscent of the staircase phenomenon was found by Goteling Vinnis in the radial pulse tracing of a patient

Regarding the underlying mechanism of the stronger first post extrasystolic beat the greater degree of diastolic filling is the most important factor In certain conditions however this explanation cannot hold good for instance in the case of interpolated extrasystoles followed by a post-extrasystolic beat with increased amplitude Busquet and Tiffeneau put forward good reasons for the assumption that in such circumstances the phenomenon is due to an increase in contractility whereas an increase in excitability could be excluded

Regarding the Q T interval of the first post extrasystolic beat *see* above (p 358)

At present the investigations of the dynamics of premature contractions and post extrasystolic beats are only of physiological interest Attempts at applying them clinically for assessing the diagnostic and prognostic significance of extrasystoles in individual cases have been made (Blumberger Blumberger and Meyer Breu and Vetter) but the premises on which the measurements of the various phases of systole and the interpretations of their results were based are open to so much doubt that at this stage the validity of this method in clinical medicine seems highly questionable

SUMMARY

The force of an artificially induced cardiac contraction is independent of the intensity of the stimulus Some apparent exceptions to this all or none law with their explanation are briefly discussed Owing to the fact that after a contraction, the heart regains its excitability gradually in the course of the relative refractory period in general an extra contraction is the weaker the earlier in diastole it occurs For the same reason an extra contraction can be elicited the earlier in diastole the stronger the extra stimulus is The refractory phase decreases in length with increasing rate and that of an extrasystole is shorter than that of normal beats The shorter total refractory period of an extrasystole elicited by an induction shock is due solely to its shorter absolute refractory period whereas the relative refractory period of an extrasystole has the same length as that of a normal beat Approximate determination of the length of the refractory period of extrasystoles in clinical electrocardiograms by measuring their Q T intervals has given conflicting results The reasons for the discrepancies are discussed and it is suggested that such investigations are devoid of any great importance The conditions in which superposition of extrasystoles may occur and the possible mechanism underlying this phenomenon are briefly reviewed Discussion of the dynamics of premature contractions is largely based on Wiggers extensive work It is pointed out that in addition to the degree of ventricular filling largely determining the force of extracontractions their mechanism differs from that of normal beats in such a way that it tends to reduce the force of an ectopic beat as compared with that of *a normal beat originating in otherwise identical conditions This aspect is* discussed in some detail

The first post-extrasystolic contraction is usually stronger than the normal beats of the individual case This is largely due to the greater degree of ventricular filling which had

taken place during the preceding longer post extrasystolic interval In certain circumstances this explanation cannot hold good for instance in the case of a larger post extrasystolic beat following an interpolated extrasystole and an increase in contractility of the heart seems the most likely explanation

It is pointed out that at present attempts at applying the experimental findings of the dynamics of premature contractions to the clinical assessment of the diagnostic or prog nostic significance of extrasystoles have not yet yielded reliable information

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INTENSITY OF ECTOPIC STIMULI

At one time the intensity of the stimulus giving rise to ectopic beats attracted much attention A brief discussion of the work on this subject is warranted because some of its results enlarged our knowledge in several important respects though most of the original conclusions have become questionable In the light of more recent work much if not most of this work requires re interpretation

The intensity of extrasystolic stimuli was frequently assessed with reference to that of the normal ones and a few salient points of the work on the latter subject must therefore be included

While the natural stimuli were originally thought to be very weak of threshold intensity (Engelmann 1894 1896 Gaskell) or of phasic threshold intensity that is responding to the phasically varying excitability of the heart (Hering 1906) a great deal of evidence accumulated subsequently which tended to show that the strength of normal stimuli was many times above threshold Amongst the numerous publications on this subject those are relevant in the context of this book which base this conclusion on a comparison between normal and artificial stimuli applied in different experimental conditions the greater strength—or qualitative superiority—of normal as compared with artificial stimuli was inferred from the observation that the heart continued to beat in response to normal impulses while artificial stimulation even with strong stimuli failed to have any effect Such observations were made on frog hearts beating under anaerobic conditions (Bachmann) or under the influence of an excess of KCl (Bunnag) the results of such studies were summarized by Asher in whose laboratory much of this work had been carried out In the same Institute it was subsequently found by Witz that local anaesthesia by novocaine of the auricle or sinus of the frog heart could produce a condition in which the normal heart action continued while the anaesthetized part failed to respond to strong artificial stimuli By a different approach Schellong—investigating the gradient of rise of the action current—arrived at the conclusion that the strength of the normal stimulus is six to eight times above threshold and in later studies with Schutz (Schellong and Schutz) found that an artificial stimulus of four times threshold intensity was effective immediately at the end of the absolute refractory period (which coincides with the end of the monophasic action current *see* section on Dynamics p 357) Schellong and Schutz assumed that a normal impulse because of its considerable intensity would if it occurred at that moment also yield a contraction This assumption was shown to be correct by Schutz and Buchthal who found that if the rate of normal impulse formation in the frog heart was increased by warming the earliest moment at which normal stimuli became effective also coincided with the end of the absolute refractory period From this it was concluded that the intensity of the normal stimuli must also be at least four times that of threshold Rothberger (1931a) observed that after interpolated extrasystoles the next supraventricular beat may start before the end of the T wave of the extrasystole in the electrocardiogram and concluded with certain reservations that the strength of the natural stimulus is considerably above threshold (*see also* p 369) A similar view was expressed by Junkmann based on the observation that auricular extrasystoles yield a contraction already at a time when strong stimuli are necessary to stimulate the ventricle directly

While the results of such investigations are of considerable interest in themselves their interpretation in regard to the intensity of natural and artificial stimuli is no longer acceptable in its original form for various reasons

(1) In all experiments discussed above induction shocks were used as artificial stimuli Such faradic shocks are of very short duration and their characteristics (for example voltage duration) were unknown A so called calibration of such currents according to an arbitrary scale (for example Kronecker units) is as meaningless in experiments of this kind as it is valueless for any general theory of excitation (Schaefer 1940)

(2) The duration of the artificial electrical stimuli was not considered

(3) The effectiveness or otherwise of natural and artificial stimuli was predominantly attributed to the intensity of the stimulus and not sufficient consideration was given to the excitability of the tissue

Amongst the studies of cardiac excitability in which a well defined electrical stimulus of known duration was used that of von Werz may be mentioned This author studied the chronaxie of the frog s ventricle during the relative refractory period (chronaxie being the minimum time during which a current of double the rheobasic strength must flow in order to excite a current has rheobasic strength if it is just capable to excite when flowing for a long time) The chronaxie is a measure of excitability inasmuch as the shorter the chronaxie the more quickly excitable the tissue In von Werz s experiments the ventricle was rhythmically stimulated (by induction shocks) and condenser discharges were applied as test shocks during the various phases of the relative refractory period It was found that immediately at the end of the absolute refractory period the chronaxie was lengthened two to three times and that it returned quickly to its original level during the relative refractory period Regarding test stimuli of the same absolute intensity von Werz also established that the longer above the utilization time their duration was the earlier in the relative refractory period did they produce an extrasystole (utilization time being the minimum time during which a current of rheobasic strength must flow in order to excite) At the end of the relative refractory period a natural stimulus of minimum intensity will be effective if its duration is at least equal to the utilization time of ventricular excitation Von Werz pointed out that because of their short duration induction shocks are inferior to natural stimuli even if the chronaxie is not lengthened and even more so if this is the case (for example because of digitalis) and concluded that the natural stimuli are of comparatively long duration but less intense than commonly believed Von Werz s results conflict with those of Asher who found no difference between the effectiveness of condenser discharges of long duration and of induction shocks Further investigations are necessary before this problem can be considered as settled

One instance of the different effect of induction shocks and of rectilinear currents is discussed in connexion with the determination of the refractory period (*see* section on Dynamics p 358)

At present we have no information about the strength (or even nature) of the natural cardiac stimulus In order to gain some insight into the intensity of stimuli necessary to elicit ectopic beats comparison was made between the effectiveness or otherwise of artificial stimuli and that of natural ones The criterion usually was whether the heart continued to beat in response to its natural impulses while artificial stimuli applied in different phases of diastole and in different experimental conditions were ineffective or vice versa (Asher and Garrey) It will be seen from what was said above that such investigations if they are to supply any information in keeping with more recent neurophysiological work on excitation must at least employ an artificial stimulus which is well defined and the strength and duration of which are known Moreover the excitability of the stimulated portion of the heart must be more fully considered than has been the case in some of the work discussed and some quantitative information about it should be available One such expression would be the chronaxie (*see* Rijlant) though its determination and that of the rheobase in the heart meets with great difficulties (Schaefer 1942)

Some of the more recent work which has a bearing on the subject under consideration

and fulfils the above conditions is discussed in the chapter on Mechanism to which the reader is referred (p 497)

Turning to the data about the presumed strength of stimuli giving rise to extrasystoles in man it has to be admitted that most of it is speculative Kaufmann and Rothberger assumed that such extra stimuli are weak just above threshold and based this opinion on the observation that in subjects with pronounced sinus arrhythmia extrasystoles tend to occur most frequently when the sinus rate is about midway between more marked tachy and bradycardia The tentative explanation was that in order for extrasystoles to occur a certain degree of sympathetic nervous tone was necessary so that extrasystoles tended to disappear whenever sympathetic tone decreased or vagal tone increased Winterberg endeavoured to explain a periodicity of cardiac rhythm consisting of periods of supra ventricular tachycardia separated by two or three slow normal beats by the assumption that the stimuli precipitating the fast series were just above threshold and that as the result of their quick succession the excitability of the heart slightly decreased so that the weak ectopic stimuli became sub threshold and the stronger normal stimuli dominated the rhythm for a few beats (In retrospect this seems to have been a case of Extrasystolie a paroxysmes tachycardiques occurring in an otherwise healthy male of twenty)

The opposite view namely that extrasystolic stimuli must have a considerable strength was put forward by Rothberger (1931b) because of the observation that interpolated extra systoles may commence before the end of the T wave of the preceding supraventricular beat had been completely inscribed In the light of more recent knowledge such observations seem far better explained by attributing them to the varying excitability of the tissues following excitation in particular to the supernormal phase of recovery and the same holds good for the observations of Rothberger (1931a) mentioned above Thus Smirk who recently published seventeen cases in which R waves interrupted T waves interpreted his observations entirely in terms of cardiac excitability

Scherf emphasized the complexity of factors which determine whether or not an ectopic focus becomes effective and stressed the importance of excitability strength of stimulus nervous influences and ionic concentration Similarly Faltitschek and Scherf attributed the presence or otherwise of an exit block in parasystole to the relationship between strength of impulse formation in the automatic ectopic centre and the excitability of the surrounding tissue (*see* chapter on Pararrhythmias p 173)

Conclusions It seems to us that neither experimental nor clinical observations make it possible to draw any reliable conclusions about the strength of a stimulus normal or ec topic Schellong s statement of 1925 still holds good As one has to measure the stimulus by its effect namely excitation and up to the present no feature of either the mechanical or the electrical manifestation of excitation can unequivocally be attributed solely to the strength of the stimulus any views about it are nothing more than suppositions (our translation)

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THE SPREAD OF THE EXCITATION OF ECTOPIC BEATS

The development of our ideas about the mode of spread of the excitation of ectopic beats reflects the gradual recognition of the great complexity of this subject which in the past appeared comparatively simple

The starting point may be placed in the work of Marchand (1877) and Engelmann (1878) who established in frogs that if a point on the heart s surface is stimulated and the action currents are led off from two places the one situated nearest to the point of stimulation becomes electrically negative in advance of the other situated at a greater distance from the site of stimulation These experiments as well as those of Burdon Sanderson and Page (1880 1884) seemed to demonstrate that if the heart is artificially stimulated the excitation starts from the point of stimulation and thence uniformly spreads in all directions

When some twenty years later the specialized conducting system was discovered Tawara (1906) expressed the opinion—which ran contrary to the conception of contemporary physiologists—that the specialized fibres conducted the impulse faster than the ordinary myocardial fibres

Kraus and Nicolai in developing this conception distinguished between normal systoles and abnormal ventricular beats (normale Systolen und abnorme Ventrikelschlage) They considered the essential difference to be that the impulses of the former were conducted in the ventricles through preformed pathways whereas the latter spread evenly in all directions without using any preformed channels of conduction (gebahnte und ungebahnte Reizausbreitung) By leading off the action currents from a series of very small areas of the cardiac surface by means of a specially designed cotton thread electrode (called differential electrode) it was subsequently established in the frog and tortoise (Clement) and in the mammalian heart (dogs and cats Erfmann) that the normal excitation activates the whole cardiac surface practically simultaneously whereas ventricular ectopic beats elicited by break shocks spread from points nearer the site of stimulation to those situated at a greater distance Rothberger and Winterberg as a result of their investigations on the shape in the electrocardiogram of ventricular extrasystoles elicited in different parts of the

dog s heart (discussed in the chapter on Localization of the Site of Origin of Extrasystoles on pp 382–4) concluded that the excitation of the ectopic beat spreads through ordinary muscle to the nearest point of the specific system whence the further conduction takes place and that it was this mode of spread which determines the electrocardiographic features

In Lewis and Rothschild s classical study (1915) on the spread of the excitation wave through the ventricles in dogs that of ectopic beats was further clarified The result of this work as far as it is relevant in the context of this book cannot be stated better than in Lewis s own words (Lewis 1925a)

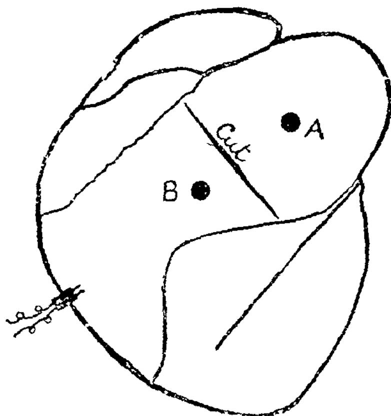


FIG 179—From Lewis *The Mechanism and Graphic Registration of the Heart Beat* Third ed 1925 Shaw and Sons London
Description in text

If an artificial wave is started by stimulating the surface of the heart in line with two electrodes the time interval between the activation of the muscle at these two contact points can be accurately determined the transmission rate calculated For different parts of the ventricular surface this rate varies It is highest and approaches or surpasses 2 000 mm per second where the muscle wall is thinnest is lowest and approaches 400 mm per second where the muscle is thickest It varies because the rate of conduction in muscle proper is slow while in Purkinje substance it is very rapid If the wall is stimulated where it is thin the artificial wave quickly penetrates the whole muscle thickness and is picked up and conveyed along the Purkinje network from which it spreads outwards through the muscle again to reach the electrodes if as in the left ventricle the wall is thick the wave may be

conducted across the superficial electrodes before it travels to the lining of the heart and out again These conclusions follow from experiment The border of the right ventricle is stimulated and an excitation wave is propagated from B to A its arrival at the two points is timed A deep cut in the muscle between the electrodes does not affect these readings a shallow cut or scratch on the endocardial surface at once delays the wave reaching B Clearly the wave passes along the endocardium over the greater part of its course (Fig 179)

If electrodes are placed on the pericardial surface (P) and on the *corresponding part* of the endocardial lining (E) and the surface is then stimulated at some distance from them (Fig 180) the wave is found *to reach the internal contact first* and if the stimulus enters far enough away *the interval between the readings at the two electrodes is precisely the same as for the natural heart* (natural readings) The wave reaches P by the path b b for that path is the quicker on account of the high conduction rate in the lining If the stimulus is applied

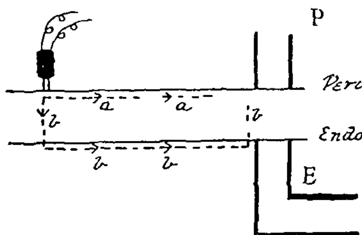


Fig 180 —From Lewis *The Mechanism and Graphic Registration of the Heart Beat* Third ed 1925 Shaw and Sons London Description in text

nearer the electrodes the wave may reach P along the path a a If the thickness of the muscle wall and the distance from the point of stimulation is known then in an experiment in which the natural readings *at the two contacts are just maintained the relative rates of con*duction in Purkinje substance and muscle can be calculated The rate is at least five times greater in the network than in the muscle The experiment is arranged so that the wave reaches P along the two paths a a and b b simultaneously the length of muscle traversed along b b is ascertained and from these data the conduction rates are calculated When the results of experiments of this and other kinds are considered it is found that in muscle the rate of conduction is about 400 mm per second in *straight* as opposed to the usual branching Purkinje strands it is approximately 4 000 mm per second

This view that the rate of conduction in the Purkinje substance is ten times that in the myocardium proper was contested by various authors on various grounds

de Boer questioned altogether that the velocity of the excitation wave is greater in the Purkinje system than in ventricular muscle and attributed Lewis s findings to the difference in temperature between the endo- and epicardial surfaces resulting from the experimental conditions This view though accepted by Abramson and Jochim cannot be considered valid (*see* Harris) Others while accepting that the Purkinje substance has a higher rate of

conduction than the myocardium proper found the former to be only 730–740 (Erlanger) or 500 mm per second (Lapicque and Veil) Both these series of experiments were however conducted under rather unphysiological conditions and cannot be expected to yield more than very approximate results Lewis remarked that Erlanger s figure is likely to be too small (Lewis 1925b) In view of the subsequent discovery of myocardial ramifications of Purkinje substance the meaning of some of these figures has become questionable Another objection based on quite different grounds was raised by Rothberger He pointed out that if the rates of conduction in the specialized system and in ventricular muscle were in the proportion 10 1 in cases of intraventricular disturbances of conduction in man initial ventricular deflections of 0 2–0 5 second would have to be found which has never been the case

If the actual velocity of conduction in the specialized system and its exact relation to that in heart muscle proper was thus controversial two main facts seemed established first that the Purkinje fibres conducted faster than the myocardium and second that a forced ventricular beat was slowly conducted through the heart muscle until it reached the nearest point of the specialized system whence the fast conduction started to the remaining parts of the ventricles In order to reach the opposite ventricle the excitation wave was assumed to travel in a retrograde direction through the ipsilateral branch of the stimulated ventricle as far as the bifurcation and thence to activate the opposite ventricle by spreading in the normal way through the contralateral main bundle branch and its ramifications

Observations on interpolated ventricular extrasystoles were in accordance with this conception As discussed in the appropriate section the first post extrasystolic beat after interpolated extrasystoles frequently shows a lengthened A V conduction time but often has a normal shape in the electrocardiogram Ashman pointed out that the blocking of the interpolated extrasystole must therefore occur either in the main stem of the bundle of His or within the A V node itself because if the blocking occurred below the bifurcation the ventricular portion of the post extrasystolic beat could not be normal but would always have to be aberrant because of altered intraventricular spread of the excitation That ventricular extrasystoles are conducted over a longer or shorter distance through the bundle branches probably as far as the A V node also follows from their effect on A V rhythm (*see* section on Extrasystoles in A V Rhythm and Return Extrasystoles p 102)

However when it became possible experimentally to produce chains of extrasystoles originating from one circumscribed focus in a ventricle and thus to put these views to experimental test some rather unexpected results were obtained For if the above conception about the mode of spread of the excitation of ventricular ectopic beats were correct severing of the bundle branch of the ipsilateral ventricle in which the ectopic beats originated should alter their shape in the electrocardiogram Contrary to expectation this did not occur whatever the method by which the chains of ectopic beats were produced

Ectopic beats in such experiments on dogs were elicited in three different ways

(1) In certain experimental conditions they could be produced by direct electrical stimulation of points on the cardiac surface of one ventricle Not only did their shape in the electrocardiogram remain unaltered after cutting the ipsilateral bundle branch between its upper and middle third but also severing of both main branches did not affect their graphic record though complete A V block ensued (Fig 181 Scherf 1926)

(2) Chains of ectopic beats were elicited by local warming of a point on a ventricle in dogs sensitized with barium Again severing of one or both bundle branches did not affect the appearance of the ectopic beats in the electrocardiogram (Scherf 1927) Occasionally after cutting both branches the initial deflections of the ectopic beats increased in duration by 0 01–0 015 second but their shape always remained the same

(3) Long chains of bigeminal heart action were produced by means of aconitine In this form too of an ectopic ventricular arrhythmia caused by true extrasystoles in the

strict sense of the term and originating in one focus of one ventricle no effect on the electrocardiographic appearance of the extrasystoles by unilateral or bilateral severing of main bundle branches was observed The coupling of the extrasystoles however showed certain analysable and instructive changes if the bundle branch of the contralateral ventricle was severed the coupling remained the same as it had been before the interference if on the other hand the bundle branch of the ipsilateral ventricle was cut the coupling increased by 0 035 to 0 04 second (*see* Fig 125) From this observation it could be concluded that the length of the coupling depended entirely upon the exact moment at which the excitation wave reaches the focus of origin of the extrasystole which moment is itself dependent, *inter alia* on the length of the path which the excitation wave utilizes to reach the extrasystolic focus (Scherf 1930)

Scherf concluded from the results of these three series of experiments that ectopic ventricular beats whether elicited by artificial stimulation or originating spontaneously in certain experimental conditions spread through the myocardium proper and do not utilize the larger branches of the specialized conducting system

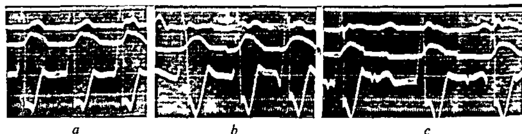


FIG 181 —From an experiment on a dog s heart *in situ* Tracings from above downward signal suspension tracing of auricle suspension tracing of ventricle electrocardiogram (ano-oesophageal lead) time base 0 02 second *a* three ectopic beats from a longer chain occurring during A V rhythm conducting system intact *b* after severing of the right bundle branch *c* after severing of the left bundle branch of the same heart The shape of the ectopic beats remains the same From SCHERF 1926 *Z ges exp Med*

A view intermediate between that of Lewis and Rothschild and that of Scherf was adopted by Drury and Mackenzie In experiments on dogs these authors produced ectopic beats in the left ventricle and recorded the arrival of the excitation wave in different portions of the right ventricle before and after cutting of the right bundle branch Such experiments demonstrated that *some* parts of the right ventricle were activated via the bundle and *some* parts via the ventricular muscle proper It should be noted that a difference of 0 005 second in the relative occurrence of laevo and dextrocardiogram is sufficient to produce noticeable changes in the electrocardiogram so that an effect of this order caused by the cutting of a bundle branch would have been traceable No effect of vagal stimulation was found on conduction either through the bundle branches or through ventricular muscle It was concluded that the mode of activation of the contralateral ventricle by an ectopic ventricular beat is the result of a race between an impulse travelling via the specialized system and one utilizing myocardial muscle

It will be appreciated that the interpretation of all the work discussed so far was based on the assumption that no communication existed between the right and left bundle branch and their arborizations The absence of such connexions was specifically mentioned by Lewis (1925c) The subsequent discovery of such links while clarifying some discrepancies revealed the great complexity of this subject

The first to demonstrate septal connexions between the Purkinje fibres of the two ventricles of the heart of calves particularly in the apical portions of the septum was Wahlin (1928 1932) Cardwell and Abramson and Abramson and Margolin confirmed this in the heart of other mammals and also showed that Purkinje fibres extended throughout the myocardium to within a few mm of the epicardial surface These were directly continuous and structurally identical with those of the subendocardium

In the light of this wider distribution of the Purkinje substance Rothberger re investigated the problem in 1933 While confirming Scherf s observations discussed above he thought that their interpretation had to be revised The failure of cutting one or both bundle branches to affect the shape of ectopic beats in the electrocardiogram could no longer be taken to indicate spread through the ventricular muscle proper as Scherf had done before the presence of septal connexions between the Purkinje network of the two ventricles was

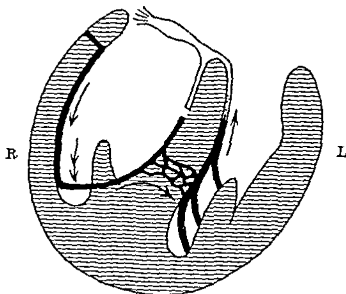


Fig 182 —The effect upon the spread of an ectopic impulse of cutting a bundle branch at different levels For further description see text From ROTHBERGER 1933 *Z ges exp Med*

known The site at which Scherf cut the bundle branches (between the upper and middle third as mentioned above) was too high to block the interseptal connexions (Fig 182) Rothberger showed that if the conducting system was severed at a point so that these were blocked a considerable widening of the initial ventricular complexes of the ectopic beats ensued (from 0 08 to 0 12 and 0 125 second) By this experimental interference the impulse *is forced to leave the specialized conducting system and travel through ventricular muscle* proper over a certain distance These experiments had also a bearing on a re interpretation of curves of so called arborization block A more detailed discussion is outside the scope of this book and the reader is referred to Rothberger and to Mahaim

The importance of the interseptal connexions for the conduction of normal as well as of ectopic ventricular impulses was also stressed by Abramson and Jochim They found that the average time consumed in the spread of an artificially induced stimulus over a constant epicardial distance on the right ventricle was only slightly less than on the left one this

observation is contrary to Lewis and Rothschild s conception that the impulse penetrates the ventricular muscle proper at a slow rate and is subsequently conducted through Purkinje substance at a much faster rate then to traverse the muscle again slowly to reach the epi cardium By obtaining the times of arrival of artificially induced ectopic impulses at various spots before and after cutting the right branch of the bundle of His evidence was found which indicated that the impulse originating on one ventricle might reach the oppo site one through the myocardial Purkinje fibres in the septum rather than over the bundle branch pathway via the bifurcation of the bundle of His (p 647) Their investigation did not support the contention of Robb and Robb that the impulse spreads through the super ficial spiral muscle in the direction from apex to base or that the superficial muscle bundles determined in any way the spread of the excitation wave

Ashman and Hull compared the widest QRS complexes seen in extrasystoles in a normal heart with those found in bundle branch block and concluded that it takes at least as long for an impulse to travel from one ventricle to the other by way of the bundle branches and bifurcation as by way of the interventricular septum They calculated that conduction of an impulse from the Purkinje network in the lateral wall of the ventricles to the bifurcation takes at least 0 035–0 04 second the delay is assumed to occur mostly in the proximal part *of the bundle branch*

A word of warning should be given against accepting too readily the existence of trans septal connexions or if their anatomical presence is considered established against over rating their physiological function As far as the anatomical work is concerned much of it was carried out by means of an injection technique which cannot be considered to give entirely reliable results The histological differentiation between specialized and ordinary myo cardial fibres is notoriously difficult Moreover results obtained in one species cannot un reservedly be applied to others In this connexion the experimental work of Alfredson and Sykes is of interest They found in experiments on calves that cutting of a bundle branch resulted in only a very slight increase (0 01 second) in the width of the QRS complex as compared to conditions prevailing in the dog and in man The most likely explanation is that in the heart of oxen functioning trans septal connexions are present which do not exist in the dog or in the human heart This view is supported by the observation that in spite of the larger size of the ox s heart the width of the QRS complex in this species is almost the same as it is in the dog and in man Further studies are necessary before the anatomical existence and physiological significance of trans septal connexions can be considered estab lished

With these reservations Rothberger s views can be said aptly to sum up the physiological significance of the trans septal Purkinje fibres According to him these fibres normally serve to activate the septum and in addition provide a safety mechanism in the event of disturbances of conduction in the bundle branches If the normal paths are intact these septal connexions are not utilized The possibility of trans septal activation in case of need may be likened to that of A V impulse formation in the event of failure of normal impulse formation in the S A node or the presence of collateral blood vessels not utilized until the normal channels of circulation fail in their proper function

It will have become apparent that the problem of the manner of spread of ectopic beats is far from solved This is understandable if the great difficulties in ascertaining the exact sequence of activation of the various portions of the ventricles in normal beats are recalled One of the main problems in this kind of work is the determination of the moment of arrival of an impulse beneath an exploring electrode that is to say the intrinsic deflection (Lewis and Rothschild p 190) Lewis s work was criticized on this account by Wiggers who used for this purpose monophasic action currents which he believed could be considered accurately to indicate the moment of arrival of an impulse beneath the exploring elec trode The validity of Wiggers method was challenged when it was found that (particularly

when Wiggers technique for obtaining monophasic action currents was used) the injured region becomes electrically positive as the result of activity of the surrounding myo cardium (Eyster Meek Goldberg and Gilson) and a more recent investigation by Harris while being partially in accord with that of Lewis and Rothschild seemed to indicate that the different size of the heart in different species is of importance regarding the intervals between the activation of the several portions of the ventricle Still more recently it has become altogether extremely doubtful whether the tip of the R wave indicates the arrival of the impulse beneath the exploring electrode and the validity of the whole method has thus been rendered highly uncertain

It seems to us that such investigations have an important bearing on the subject of this section For if the time relations of the sequence of activation in normal beats cannot yet be considered as firmly established for the reasons discussed above similar considerations hold good for any method by which it is sought directly to determine the manner of spread of ectopic beats The application to investigations about the manner of spread of ectopic beats of a method making it possible accurately to determine that of normal beats would seem to be the next step in the elucidation of this problem

SUMMARY

When the advent of electrocardiography made it possible to examine experimentally the mode of spread of the excitation wave of ectopic ventricular beats in the mammalian heart the result of such investigations was interpreted as indicating that the excitation spreads slowly through ventricular muscle from the point of stimulation to the nearest portion of the specialized conducting system thence travelling at a much higher rate in a retrograde direc tion through specialized tissue as far as the bifurcation (or the A V node) and activating the opposite ventricle by spreading through the main bundle branch and its ramifications of the contra lateral ventricle and finally traversing at a slow rate its ventricular muscle proper from within outwards It was believed that the rate of conduction in ventricular muscle proper was considerably lower than in the Purkinje substance but differences of opinion existed as to the relation between the two rates of conduction and regarding the velocity of spread through the Purkinje network The failure by cutting one or both main bundle branches to affect the shape in the electrocardiogram of artificially elicited or of spontaneous ventri cular ectopic beats was first interpreted as indicating that the ectopic impulse utilizes only ventricular muscle in order to reach the opposite ventricle This view had to be abandoned in the light of the subsequent discovery of trans septal connexions between the Purkinje network of the two ventricles The further discovery that Purkinje fibres continuous and structurally identical with the subendocardial ones extended throughout the myocardium to within a few mms of the epicardial surface created further difficulties in any longer accepting the view that conduction through ventricular muscle was much slower than through the specialized conducting system Re investigation of the sequence of surface acti vation by means of monophasic action currents suggested the necessity of revising our con ceptions about the spread of normal excitation to the various portions of the ventricular surface which contrary to previous views seems to be activated practically simultaneously in its entirety (except for one small portion) As the result of later investigations this view was challenged on technical grounds The doubts which have been cast by these more recent anatomical and physiological studies upon the views about the mode of spread of ectopic impulses through the mammalian heart are so great that this problem cannot be considered as clarified The present state of our knowledge may be summed up by the following tentative suggestion which does not seem to conflict with any established facts If the conducting system is intact the ectopic impulse spreads from the point of origin through ventricular muscle proper and the myocardial ramifications of Purkinje substance

to and through the ipsilateral main bundle branch as far as the bifurcation and thence activates the opposite ventricle through normal pathways the rate of conduction through ventricular muscle proper is however not so much slower than in the specialized conducting system as originally believed In the event of interruption of conduction in one or both main bundle branches the excitation wave utilizes trans septal connexions between the Purkinje networks of the two sides In case of impairment but not complete interruption of normal conduction the activation of the opposite ventricle is the result of a race of the excitation wave travelling through the bundle branches on the one hand and through trans septal connexions on the other

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MISCELLANEOUS PHYSIOLOGICAL CONDITIONS

Extrasystoles in Animals

Though our knowledge about the occurrence of extrasystoles in normal animals and in association with various diseases is scanty it can be said that spontaneous ectopic arrhythmias are certainly uncommon in most animals used in laboratory experiments since otherwise their presence would have been reported far more frequently

One possible exception are rabbits which sometimes show spontaneous extrasystoles and which are prone to develop this type of arrhythmia as a result of drugs and vagal re flexes Regarding the former morphine should be mentioned especially (Ken Kure Hering) regarding the latter the reader is referred to the chapter on Extrasystoles and the Nervous System

As far as dogs are concerned in more than one thousand experiments on animals anaesthetized with ether or a barbiturate we did not encounter one single instance of spon taneous extrasystoles Lannek considers even single auricular or ventricular extrasystoles as definitely pathological and comparable in this respect to heart block

In the horse extrasystoles are uncommon (Lewis) and seem to have a similar significance Amongst a hundred cases of arrhythmias observed in horses Norr encountered fifteen instances of extrasystoles 40 per cent of which took a fatal course Auricular atrio ventricular and ventricular types were recorded If they occurred during an infection of which pneumonia tonsillitis and gastro enteritis are mentioned the extrasystoles sometimes disappeared when the infection had subsided Anatomically gross pathological lesions were found in four horses In only one case were extrasystoles encountered in a healthy animal In the horse extrasystoles are much rarer than disturbances of atrio ventricular conduction which were four times as frequent and were often found in otherwise healthy and strong animals Auricular fibrillation has been reported by several authors (Lewis Norr Roos)

Extrasystoles in only One Auricle

Extrasystoles confined to only one auricle have been reported in experimental conditions in which such premature beats were induced by induction shocks in an auricle after inter auricular conduction had been abolished (Scherf and Siedek)

Fig 183 provides an example of such an observation made on a dog Both vagi had been severed and as the resulting sinus tachycardia made the study of auricular activity impossible complete A V block was produced by clamping the bundle of His After the sinus node had been separated from the right auricle by means of small ligatures applied between the A V border and the angle between the superior vena cava and the right auri cular appendage inter auricular block was observed The right auricle beat at a rate of 111 per minute (cycle length 0 54 second) the left independently from the right at 120 per minute (cycle length 0 50 second) An extrasystole elicited in the right auricle by an induc tion shock was not conducted to the left auricle The post extrasystolic interval equalled the spontaneous right auricular cycle length which indicates that the site of origin of the extrasystole was at or near the site of the spontaneous impulse formation activating the

right auricle In these experiments extrasystoles precipitated from the left auricle remained confined to this chamber the post extrasystolic interval being slightly longer than the spontaneous left auricular cycle length but not being compensatory Auricular flutter confined to one auricle could also be produced in this series of experiments

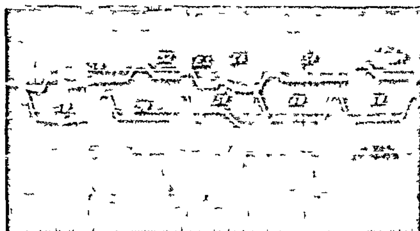


FIG 183 —From an experiment on a dog Tracings from above downward indicate signal of stimulation suspension curves of right auricle and left auricle electrocardiogram (ano oesophageal lead) time base 0 02 second The P waves of the left auricle have deeply inverted initial deflections followed by an upright final deflection those of the right auricle have a similar con figuration but are much smaller The extrasystole elicited in the right auricle is not transmitted to the left auricle From Scherf and Siedek *Z Klin Med*

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CHAPTER X

THE LOCALIZATION OF THE SITE OF ORIGIN OF EXTRASYSTOLES

INTRODUCTORY REMARKS

To a certain degree localization of the site of origin of extrasystoles became possible in the pre electrocardiographic era at an early stage of the work on extrasystolic arrhythmias The analysis of arterial and venous pulse tracings and mechanical cardiograms made possible the distinction between extrasystoles arising in the ventricle auricle A V node and S A node With the advent of electrocardiography this work was on the whole confirmed though in regard to some details previous conceptions were demonstrated to be based on fallacious interpretation of mechanical records and errors could be rectified The misinterpretation of atrio ventricular extrasystoles as ventricular extrasystoles with retrograde conduction to the auricles may be cited as an instance (*see* section on Atrio Ventricular Extrasystoles p 168) But electrocardiography was expected to achieve far more than this accurate localization of the site of origin of extrasystoles that is in right or left auricle or ventricle and even accurate delimitation of the area within an auricle or ventricle was hoped for In spite of much work and thought spent on this problem progress was disappointingly slow results contradictory and even now this aspect of ectopic arrhythmias is far from solved

Up to quite recently it could justifiably be said that determination of the site of origin of extrasystoles had only an academic if any importance and that such studies were devoid of any general physiological or practical clinical value That this view is no longer tenable will become apparent later in this chapter

VENTRICULAR EXTRASYSTOLES

The various stages in the development of our ideas about the site of origin of ventricular extrasystoles can conveniently if arbitrarily be divided into four periods the first from the investigations of Kraus and Nicolai starting in 1907 up to those of Rothberger and Winterberg in 1913 and of Lewis in 1916 the second from 1913 to 1930 when the observations of Barker Macleod and Alexander on an exposed heart in man threw doubt on the views held in the preceding period the third until about 1940 when the experimental observations of Nahum and Hoff started which if confirmed would reveal sources of error in past investigations and make necessary reconsideration of views about the origin of deflections in the electrocardiogram and the present phase dating from about 1940

First Period 1907–1913

The first period is now mainly of historical interest Kraus and Nicolai (1907) employing only one lead often without even stating accurately which one was used found in dogs that in extrasystoles from the right ventricle the main initial deflection was directed upwards in those from the left ventricle downwards and interpreted their findings as indicating contraction only of the one stimulated ventricle hemisystole which they wrote they had established with complete certainty (welches wir völlig sichergestellt haben) The differences in the electrocardiogram were most pronounced if the heart was stimulated apically as far

to the left as possible and basally as far to the right as possible (Nicolai and Rehfisch 1908) It is an instructive lesson certainly of more than historical interest that this complete certainty had to be partially questioned by the authors themselves as soon as the following year (Kraus and Nicolai 1908) One year later Nicolai (1909) admitted that it was only possible to determine experimentally whether the abnormal contraction started in the right or left ventricle something he considered akin to hemisystole and in their monograph on the electrocardiogram Kraus and Nicolai in 1910 gave up the idea of hemisystole altogether For Hering (1910) had concluded from his investigations that the direction of the initial deflection of extrasystoles depended on whether they were elicited from apex or base and not whether they originated in the right or left ventricle he used lead 1

Nicolai (1909) and Kraus and Nicolai (1910) distinguished three different types of extrasystoles type A originating in the apical portion type B arising in the basal parts and type C a central type originating in an intermediate zone In a lead from the right auricle and the left apex the initial deflections of type A were directed downwards of B upwards To a certain extent the types A and B could according to Kraus and Nicolai also be ascribed to the left and right ventricle respectively This was supposed to be only accidental (p 164) and due to the fact that the anterior basal portion was predominantly formed by the right and the apical by the left ventricle In a later section of the same book (p 302/3) however, the relation of these two types to left and right ventricular origin was stressed There is considerable confusion in these writings whether the different direction of the deflections of extrasystoles indicates a left/right ventricular or apical/basal origin Kahn (1909) on the other hand definitely expressed himself in favour of the former and rejected the latter alternative He found that in lead 1 extrasystoles from the base and the apex of the right ventricle were directed upwards and those from the left apex in the opposite direction Results with lead 3 were inconclusive In later experiments (1910) he included for the first time the posterior aspect of the heart in such investigations and using lead 2 arrived at the same interpretation

Rothberger and Winterberg (1910) examined the shape in the electrocardiogram of extrasystoles elicited mechanically in dogs using an ano oesophageal lead which closely corresponds to lead 3 In precipitating extrasystoles along a line running from the anterior border of the right auricular appendage to the apex the deflections were upright when precipitated from the first three points all belonging to the right ventricle and downward in the case of apical extrasystoles The direction changed as the line along which the points of stimulation were situated crossed the coronary sulcus Rothberger and Winterberg also showed that from an intermediate zone extrasystoles could be elicited which had an almost normal form in the electrocardiogram The explanation based on the view of Eppinger and Rothberger (1909) that the normal electrocardiogram is the resultant of two antagonistic forces was that an artificial stimulus so placed that it activates the ventricles in the same succession as the normal impulse yields an electrocardiogram which resembles that of normal beats Similar views about the origin of the normal electrocardiogram were expressed by Nicolai and Rehfisch (1908) and Selenin (1911) They are considered to deserve a brief reference as they anticipate by a considerable number of years the conception of the dual nature of the normal electrocardiogram which was later stressed by Lewis in 1916

The main criticism of these earlier investigations is that the importance of the lead used for recording the action currents was not appreciated This is the more noteworthy as Einthoven fully realized this as early as 1908 He stated that regarding the site of origin of extrasystoles lead 1 distinguishes between right and left half of the heart and lead 3 between apical and basal portions Upward directed deflections in lead 1 indicated origin in the right downward ones in the left half of the heart upward and downward directed deflections in lead 3 were interpreted as signifying basal and apical origin respectively

Second Period 1913–1930

With the re investigation on a large scale of this subject by Rothberger and Winterberg in 1913 work on this problem entered a new phase—the second part of our arbitrary division In experiments on dogs extrasystoles were elicited from many points of the exposed heart and their shape in the electrocardiogram studied lead I and the ano oesophageal lead being recorded in immediate succession The main results regarding the direction of the initial ventricular deflections were

1 Extrasystoles from the anterior surface of the left ventricle near auricular appendage at the base downward in lead I mainly upward in ano oesophageal (a–o) lead

2 Extr asystoles elicited from a line starting at the left auricular appendage and running across the heart at equal distance from the apex upright throughout in a o lead in lead I changing from downward to upright at about a point where the above line crossed the coronary ul cus

3 Extrasystoles precipitated from a line running from the left auricular appendage to apex downward throughout in lead I in a o lead at first upright but the height of the deflection decreased and an S wave of gradually increasing depth developed as the point of stimulation approached the apex the direction of the T waves also became gradually reversed and from the apex typical left extrasystoles were obtained that is the initial deflections being directed downward followed by high upright T waves

4 Extrasystoles from the posterior surface usually the initial deflections were directed downward in both leads but on crossing the interventricular sulcus from the left auricular appendage in the direction of the right ventricle they became upright in lead I The degree of rotation of the heart around its longitudinal axis was found to be of paramount importance

5 Extrasystoles from the right ventricle precipitated from a line running from the middle of the right cardiac border to the apex and left border upright in lead I as far as the coronary sulcus thence smaller deflections until they became directed downward from points of the left cardiac border In the a o lead transition also occurred at the coronary sulcus and it was noted that basal extrasystoles (that is upward) were obtained from an area near the apex

These extensive investigations showed that the direction in the electrocardiogram of the initial deflections of ventricular extrasystoles could not unreservedly be assumed to indicate whether they originated either in the right or the left ventricle or in the basal or apical portion of a ventricle It is true that regarding lead I the dividing line on the anterior surface between right and left ventricular extrasystoles ran along the coronary sulcus but this was the case only in the more cranial portion More caudally the line deviated to the left so that extrasystoles from the right portion of the apex of the left ventricle yielded right shapes On the posterior surface the dividing line coincided more closely with the interventricular sulcus particularly in its basal portions but the degree of rotation of the heart had a decisive influence on the electrocardiographic appearance of the extrasystoles Regarding the a o lead no sharp dividing line between right and left or apical and basal extrasystoles was found on the anterior surface and an extensive zone yielded atypical complexes extrasystoles from the posterior surface showed in this lead left (that is downward directed) initial deflections except for a part at the base of the right ventricle in which they had the opposite direction

The conclusion of Rothberger and Winterberg was that the appearance in the electro cardiogram of ventricular extrasystoles did not depend on the relation of the stimulated point either to right or left ventricle or to the distance from the midline but probably depended on which muscular portions were first activated from the stimulated area Based on Nicolai s views about the distinction between spread of excitation through muscle and

that through the specialized conduction system Rothberger and Winterberg thought that the location of the stimulated point in relation to the point of the specialized system whence the further spread of the excitation took place was the factor decisive for the appearance in the electrocardiogram of the forced beats

Lewis whose views on the subject were to determine for many years the conceptions about the site of origin of extrasystoles arrived at the same conclusions In experiments on dogs (1916) he stimulated numerous (fourteen) points on the anterior surface of the right and left ventricle and using an axial lead (lead 2) found the main initial deflection directed upward in extrasystoles elicited from the right and downward in those from the left ventricle No two stimulated points yielded identical deflections but the nearer the points the closer was the resemblance in the record On crossing the descending branch of the left coronary artery the type of complex in the electrocardiogram changed abruptly This was attributed to the change in the side of the Purkinje network through which the impulse spread By stimulation of a point immediately to the left of the coronary sulcus intermediate forms were recorded closely resembling the complexes of normal beats This observation confirming that of Rothberger and Winterberg (1910) was explained by assuming that the excitation wave of the ventricular extrasystole spread through the Purkinje network of both the adjacent ventricles in a fashion similar to that of supraventricular beats The study of such extrasystoles arising near a septum has recently attracted special interest (*see* below)

Applying these experimental observations in which lead 2 was used (Lewis 1925a) to the interpretation of human curves Lewis considered extrasystoles with upright initial deflections in lead 2 as arising in the right ventricle those with a downward one as left ventricular in origin The examples reproduced by him (Lewis 1925b) indicate that downward initial deflections in lead 1 and upright ones in lead 3 were considered to indicate right ventricular origin while downward complexes in all three leads in an instance of left ventricular extrasystoles were considered atypical left ventricular extrasystoles were expected to yield upright deflections in lead 1 and downward ones in lead 3 Although Lewis himself pointed out at the time that it was impossible to localize spontaneous extrasystoles more than approximately and warned against applying to human records findings obtained in the dog heart the above interpretation went unchallenged for many years For Lewis s reading seemed to accord well with the electrocardiographic features of other conditions producing a predominantly left or right ventricular effect Regarding the former left ventricular preponderance in cases of hypertension or aortic valvular disease and what was then believed to be right bundle branch block (old terminology) may be cited as instances in these conditions too the main initial deflections were usually directed upwards in lead 1 and downward in lead 3 Similarly predominating right ventricular effects were recorded as right ventricular preponderance in cases of mitral stenosis or chronic *cor pulmonale* or in cases of what was then thought to be left bundle branch block (old terminology) such tracings showed the main initial deflections directed downward in lead 1 and upward in lead 3 the right ventricular origin of extrasystoles displaying such features seemed thus hardly questionable It will be shown below however (p 386) that all these interpretations had subsequently to be reconsidered

Another line of approach to this problem was provided by *investigating the shape in the electrocardiogram of ectopic beats elicited in man* when the heart had become accessible for such studies Considerable sources of error are present in such investigations as if the heart was not exposed at operation accurate localization of the stimulated point is not possible and if the exposed heart was used the very fact of exposure is likely to have influenced the electrocardiographic appearance of extrasystoles by altering the contact between the heart and surrounding structures In both instances an abnormal position of the heart has to be considered as a further important source of error and lastly an abnormal condition of the

heart itself has to be excluded With these reservations the most important papers on the subject may be briefly reviewed

In a patient Hoffmann (1913) stimulated mechanically the heart which after rib re section was covered only by soft tissues and found that the initial ventricular deflections of the forced beats were directed downward in lead 1 and upward in lead 3 whatever the place of the mechanical stimulation was The published data are inadequate for any detailed analysis

A similar study was carried out in 1927 by Oppenheimer and Stewart in a man of sixty with marked scoliosis with its convexity to the left in whom the lateral portions of the second to the eighth left ribs had been resected for empyema Auricular and forcible ventri cular contractions were visible through the chest wall and helpful regarding the location of the mechanical stimuli (strokes with a percussion hammer) The presence of bradycardia due to complete A V block facilitated effective stimulation Eight points were selected four as much as possible to the left and four along the left sternal border as near as possible to the midline If a point believed by the investigators to belong to the right ventricle was stimu lated the initial deflections of the forced beats were directed upward in lead 3 opposite direction was found in extrasystoles elicited from areas believed to be situated in the left ventricle It is however noteworthy that the small deflections in lead 1 hardly referred to by Oppenheimer and Stewart were always directed downward which according to present views tends to indicate left ventricular origin This possibility also considered by the authors of the paper became important in connexion with the subsequent work of Barker Macleod and Alexander referred to below Oppenheimer and Stewart s tracings also show that in lead 3 stimulation of points lying closer to the base yielded upright deflections those situated near the apex downward excursions these results are in agreement with Ein thoven s conceptions mentioned above Apart from the inaccuracy of the location of the stimulated points the main doubts about the validity of the results arise from the abnormal position of the heart and from the possibility of a pathological condition of the myocardium and/or conducting system made probable by the presence of complete A V block

A similar observation made by Fossier (1928) on a man of thirty nine with congenital absence of the lower half of the sternum also was in agreement with Einthoven s views about the localizing significance of lead 3 Six points were stimulated by tapping with a hammer points 1–4 being situated below one another on the anterior surface at distances of 3 cm point 5 being far to the right and 6 as far left as possible The conclusions were that pre mature contractions the initial deflections of which were upright in leads 2 and 3 originate from the basal portions while the opposite direction denotes apical origin

Third Period 1930–1940

These investigations in man did not arouse much interest until Barker Macleod and Alexander published in 1930 their observations on the results of artificial extrasystoles induced by induction shocks in the heart of a man of thirty which had been exposed for pericardiostomy because of suppurative pericarditis complicating streptococcal pneumonia Twelve points on the surface of the heart were stimulated through an opening in the peri cardium 6 × 4 cm Subsequent necropsy showed the heart to have been essentially normal In all curves of forced beats from the right ventricle the initial deflections were upright in lead 1 they were downward in extrasystoles from the left ventricle It was thought that the direction of the deflections depended on whether the Purkinje system of the right or of the left ventricle became activated in advance of that of the other The position of the excited point relative to the cephalic or caudal aspect of the heart manifested itself in leads 2 and 3 as the cephalic aspect was approached the chief deflections in these leads tended to become upright Lead 1 therefore indicated from which ventricle the extrasystoles had arisen and

leads 2 and 3 (particularly 2) signified the level of the focus of origin with reference to the long axis of the body These views are remarkably similar to those put forward by Einthoven more than twenty years earlier

To a certain extent these results are also in accordance with those obtained experimentally by Rothberger and Winterberg (1913) They can also be reconciled with those of Fossier after a slight re interpretation of this author s findings and with those of Oppenheimer and Stewart if their curves are considered to have been obtained from the left ventricle which is very possible (*see* above)

The main importance of the study of Barker Macleod and Alexander lay in the fact that their discordant curves were not in agreement with the views then held generally (The term discordant signifies opposite direction of the main deflections in leads 1 and 3 whereas identical direction of these deflections is termed concordant) If discordant curves with upright deflections in lead 1 were yielded by right ventricular extrasystoles the conclusion became inevitable that these features up to then considered to be a left ventricular effect actually were right ventricular ones A similar reversion of interpretation applied to discordant curves with downward deflections in lead 1 and such tracings had now to be assumed to be left ventricular effects The findings of Barker and collaborators had therefore a significance far exceeding that of localization of the focus of origin of extrasystoles They led to a re interpretation of the curves obtained in cases of bundle branch block and to a new explanation of those indicating right or left ventricular preponderance

The inference regarding bundle branch block was that if discordant curves with initial deflections directed upward in lead 1—the common type—were a right ventricular effect bundle branch block curves of this kind indicate left bundle branch block and those with downward directed deflections in lead 1 right bundle branch block—a reversion of the terminology generally accepted up to that time This view was supported by Wilson Macleod and Barker By means of semidirect leads from the surface of the dog s heart with bundle branch block and by serial precordial leads in subjects with bundle branch block tracings were obtained which demonstrated that the common type of bundle branch block was a block of the *left* bundle branch As far as preponderance curves were concerned it could not be questioned that in cases of hypertrophy of the left ventricle discordant curves with upright deflections in lead 1 were encountered in the majority of cases If such tracings had now to be considered as representing right ventricular effects a new explanation for their occurrence in cases of left ventricular hypertrophy had to be sought This consisted in the assumption that in such cases the spread of the excitation wave through the hypertrophied left ventricular wall resulted in a delay of the spread of impulse with the result that the first portion of the initial ventricular deflections was determined by the right ventricle displacement of the septum to the right and rotation of the heart were further factors responsible for the electrocardiographic features

This reversal of terminology regarding focus of origin of extrasystoles as well as that of bundle branch block has become generally accepted Objections were first raised by Rothberger (1933) who compared the shape of extrasystoles obtained in experiments by him with Winterberg (1913) with those in which one main bundle branch and all divisions except one of the other branch were cut (Rothberger and Winterberg 1917) and concluded that the old terminology was correct He also stressed the difference in structure and position of the heart of the dog compared with the human and the necessity of very thorough and expert histological examinations of the specialized system in cases of bundle branch block in man in which a correlation between electrocardiographic and anatomical findings was desired

While some of Rothberger s arguments are valid in themselves his conclusions have not *been borne out by subsequent developments* Above all the findings obtained by Barker and collaborators as a result of stimulation of various points of the exposed human heart were confirmed in similar cases by several authors (Marvin and Oughterson 1932 electrical

stimulation of one point each of the anterior and posterior surfaces of the heart in a man of thirty eight with right sided empyema and pericarditis Padilla and Cossio 1932 by mechanical puncture of the right ventricle in a patient with Hodgkins disease Vander Veer 1933 mechanical stimulation of the right ventricle in a boy of eleven operated for Pick s syndrome Lundy and Bacon 1933 in a boy of four with purulent pericardial effusion electrical stimulation of two points on the left ventricle one near its base on the lateral posterior border the other near the apex both yielded discordant tracings from the first point the deflection being upright in lead 1 and downward in lead 3 from the apical point the reverse)

The revised terminology was also supported by experimental work amongst which the extensive investigations by Storm (1936) on Javanese monkeys (*macaca irus*) should be mentioned in some detail since Storm s monograph is an important contribution and not easily accessible Storm points out that much of the work on this subject had been unsatisfactory or at least not entirely convincing for the following reasons

1 An insufficient number of leads were taken or the type of lead employed was not indicated

2 Leads were used in experimental work which were not comparable to those used in clinical practice (for example ano oesophageal or direct leads)

3 The three limb leads were not recorded simultaneously

4 The heart was in an abnormal position (for instance because of the thorax having been opened or pathological conditions being present in the surrounding structures)

5 The contact between the heart and surrounding structures was inadequate or variable (for instance resulting from opening the thorax)

6 The stimulus was not sufficiently localized

7 An insufficient number of points were stimulated

8 The stimulus was applied on the surface whereas deeper layers should have been used

9 The applicability to conditions in man of results obtained in some of the experimental work is doubtful

10 The heart was in a pathological condition

Storm took great pains to avoid these pitfalls In twelve monkeys he stimulated by means of induction shocks eighty six different points on the anterior and posterior surfaces of the heart the thorax being closed and respiration being spontaneous The three standard leads were recorded simultaneously His results were as follows

1 The initial deflections in lead 1 of all premature beats originating in the right ventricle were directed upwards of those originating in the left ventricle downwards

2 The initial deflections in leads 2 and 3 of all premature beats originating from the base were directed upwards of those originating in the apex downwards irrespective of whether they were elicited from the right or the left ventricle

3 As the point of stimulation was moved from the apex towards the base an intermediate zone was found in which the initial deflections changed from a downward to an upright direction

4 Generally the ectopic beats showed a pure diphasic form consisting of an initial and final deflection the latter being in an opposite direction to the former but beats elicited from the region of the interventricular groove showed polyphasic features often having some resemblance to complexes of normal beats

5 Ectopic beats originating in corresponding points of the anterior and posterior surface of the heart showed as a rule similar features in the electrocardiogram

These conclusions support the revision of Lewis s terminology and are in accordance with the older work of Einthoven

In the light of recent developments Storm s statement is of particular interest that his results conflict with the opinion of Lewis that in the case of ventricular premature beats activation of the ventricular wall just as in the case of the normal contraction always proceeds from within outwards and in the same way (Storm p 179) In Storm s opinion Lewis s observations are better explained on the basis of the old interference theory, that is by assuming that negativity of the ventricular wall starts at the point of stimulation irres pective of whether that negativity had travelled from within outwards or in the reverse direction By way of comment we should like to point out that Storm s account of Lewis s work seems incomplete since Lewis fully considered direct spread through muscle (*see* section on Spread p 371)

By a different ingenious method designed by Battro Braun Menendez and Orias for investigating patients with bundle branch block Castex Battro and González (1941) obtained results which were in accordance with Barker and collaborators as far as lead I is concerned The method is based on detecting and analysing the asynchronism between the contraction of the two ventricles by simultaneously recording electrocardiogram phono cardiogram and central arterial or venous pulse Out of twenty three cases of spontaneous extrasystoles examined in this way ten showed downward and thirteen upright deflections in lead I and by the above method it was found that those with a downward deflection arose in the left ventricle whereas upright deflection was associated with origin in the right ventricle

Other investigations while essentially confirming the view of Barker and collaborators lead to the recognition of various complicating factors

The patient investigated by Prinzmetal Oppenheimer and Dack (1937) a man of thirty eight with constrictive pericarditis and a right sided hydrothorax had right axis deviation in the electrocardiogram During the second of two operations for partial pericardiectomy extrasystoles elicited from the left ventricle about 3 cm to the left of the septum yielded small upright deflections in lead 1 and upright deflections in lead 3 the two leads being simultaneously recorded Subsequently some time after operation extrasystoles were precipitated through the chest wall by tapping and since at operation the right ventricle had been noticed to form nearly the whole area in contact with the anterior chest wall it seems reasonable to assume that such extrasystoles originated in the right ventricle In three of the four stimulated points the extrasystoles gave deflections which were directed downwards in lead 1 and upwards in lead 3 the opposite was found only in the fourth point situated fur thest caudad These findings do not conform with the new terminology Prinzmetal and his collaborators attribute this discrepancy to the presence of right axis deviation and claim that the new nomenclature seems applicable only if the direction of the electrical axis is normal or if there is left axis deviation Similar discrepancies due to the same factor seem to have been present in the case of Lundy and Bacon (*see* above) and possibly in that of Oppenheimer and Stewart (*see* above) The fact that at the first experiment the heart was exposed whereas at the subsequent one it was covered may also have contributed to the different results obtained by Prinzmetal Oppenheimer and Dack

By eliciting extrasystoles from the points used by Barker and collaborators Kountz Prinzmetal Pearson and Koenig (1935) confirmed in human hearts revived immediately after death the findings of Wilson and collaborators regarding bundle branch block tracings and with unimportant exceptions those of Barker and collaborators regarding extrasystoles By shifting the heart they also confirmed Barker s prediction that what was right axis deviation in the old terminology actually is left axis deviation and vice versa In cases in which there was right axis deviation (old terminology) because of an abnormal position of the heart or of failure of a portion of the left heart to revive the tracings of bundle branch block may be reversed The last observation in accordance with those of Prinzmetal Oppenheimer and Dack on the living subject (discussed above) emphasizes the importance

of the direction of the electrical axis in such determinations Rotation of the heart was also found to be of importance

Further investigations of Kountz Prinzmetal and Smith (1935a) were directed to clarify the differences in observations on the heart of dogs and of human beings By accurately placing dogs hearts into the human thorax these authors confirmed the findings of Barker and collaborators regarding bundle branch block and extrasystoles Some differences were found to be due to the different configuration of the chest in the dog as compared with that in man since in the dog the thorax is deeper and on opening the chest the heart falls back into the posterior mediastinum This accounts for certain changes in the experimental findings on these two species not only because of differences in the position of the heart but also as a result of altered contact between the heart and surrounding structures In monkeys whose chest resembles more the human one than that of dogs the above results were confirmed (Kountz Prinzmetal and Smith 1935b)

The importance of the position of the heart also becomes evident from the investigations of Abramson Katz Margolin and Lourie (1937) In experiments on monkeys and dogs they mapped out lines of transition regarding the direction of the initial and the final deflections of forced beats By short step-like movements of the stimulating electrodes these authors elicited extrasystoles from many points in close proximity to one another Such lines of transition were found not to conform with any anatomical boundaries on the surface of the two ventricles Localization of extrasystoles regarding right or left ventricle was found not possible from lead 1 and the configuration in lead 3 depended essentially on whether the anterior or posterior surface of the heart was stimulated No diagnostic significance was found to be attached to concordancy or discordancy of the tracings and such terms were considered superfluous With rotation of the heart around its long axis the lines of transition remained practically unaltered in relation to the long axis of the body (that is the lines shifted correspondingly on the surface of the heart) whereas with other types of change of position (moving apex to right or left without rotation or displacement of the apex sternad or vertebrad) the lines of transition remained unchanged in relation to the surface of the heart and shifted correspondingly relative to the long axis of the body Another point of interest is that such lines of transition could be modified by a shunt between the heart and the axilla or by interposing an insulator between the posterior surface of the heart and the muscles illustrating the importance of the structure of the surrounding media Some of these results had previously been obtained in cats by Abramson and Weinstein (1936)

Katz and Ackerman (1932) had gone so far as to declare impossible any localization of the focus of origin of extrasystoles and Kissin Ackerman and Katz (1933) expressing a similar view regarding bundle branch block tracings in man suggested that the interpretation should be confined to diagnosing bundle branch block configuration This scepticism seems to go too far for even if the shape of the complexes in the tracings is materially changed by an altered position of the heart the direction of the main deflections often remains the same Moreover Foster (1935) pointed out that the degree of change of position found necessary experimentally to produce such electrocardiographic variations in bundle branch block was often excessive Further objections to applying to the localization of the focus of origin of extrasystoles interpretation of bundle branch block tracings will be discussed below To base such localization on determining the electrical axis of extrasystoles and correlating it with that of sinus beats (Baumann and Weber 1935 v Unghvary 1938) has so far not proved a satisfactory or practicable method An attempt at localizing the site of impulse formation of ventricular extrasystoles in terms of the affected muscle bundle (superficial bulbo spiral and superficial sino spiral muscles) (Robb Robb and Hiss 1935) was as unsuccessful as a similar endeavour of the same school of workers to explain on the same basis the mode of spread of the excitation through the myocardium (*see* section on Spread p 376)

The stage reached at that time aptly surveyed by Moia and Batlle (1937) can be *sum marized* thus On the whole most of the work was in accordance with Rothberger and Winterberg s results obtained in dogs in 1913 Contrary to Lewis s view with the heart in a normal position extrasystoles originating in the right ventricle generally yield upright deflections in lead 1 and left ventricular extrasystoles downward deflections in lead 1 in both instances the tracings can be concordant or discordant according to the situation of the stimulated point The reversal of the old terminology resulting from the work of Barker and collaborators had become generally accepted discordant curves with upright initial deflections in lead 1 and downward ones in lead 3 previously considered to denote a left ventricular effect actually were right ventricular ones and vice versa and this reversal was applied to the location of the focus of origin of extrasystoles and to the side of the lesion in bundle branch block Lead 3 permits only differentiation between basal or apical origin Therefore extrasystoles originating in either ventricle may show concordant or discordant tracings The importance of the position of the heart and of the structure of surrounding tissues was realized But the picture as a whole was still confused and confusing In par ticular the meaning of discordant and concordant tracings was obscure some exceptions of experimental results regarding the occurrence of left or right ventricular extrasystoles elicited from portions of the contralateral ventricle could not be satisfactorily explained and the applicability of findings obtained in cases of bundle branch block to those of extrasystoles and vice versa was not entirely clarified

Fourth Period, Since 1940

At this stage the extensive investigations of Nahum Hoff and collaborators started which we took as marking the beginning of our fourth period This work if confirmed would not only throw light on some of the above questions but also as will be shown would re open some allied problems of cardiac physiology which have a bearing on the principles of the genesis and interpretation of electrocardiograms While this work is of sufficient impor tance to warrant a detailed discussion in this monograph it should be emphasized at the start that at present it has not been confirmed and that the views of Nahum Hoff and collaborators are not supported by the results of vectoranalysis and vectorcardiography These contradictions are pointed out later in this chapter (p 397) after the investigations of this school of workers have been discussed

These studies started by a re investigation of the influence of the right and left ventricle on the electrocardiogram (Hoff Nahum and Kisch 1941) By means of surface application of a M/10 or M/5 solution of KCl these workers claimed to have eliminated in experiments on dogs the surface electrical activity of certain parts of the heart and in this way to be able to obtain dextro- and laevocardiograms By warming or cooling the right or left ventricle and by eliciting extrasystoles from symmetrically located points equidistant to the right or left from the septum they obtained asynchronism in the contraction between the right and left ventricle and concluded that the upstroke of the R wave is formed by the up-stroke of the dextrocardiogram whereas the downstroke is due to the laevocardiogram Extrasystoles precipitated from the left ventricle yielded downward deflections in all three conventional leads provided that the point of stimulation was sufficiently removed from the septum for the excitation to activate the greater part of the left ventricle before reaching the right one Extrasystoles from the right ventricle yielded upright initial deflections in the three leads (Nahum Hoff and Kaufman 1941a) with similar qualifications regarding activa tion of most of the right ventricle in advance of that of the left (*see* below) If a KCl pledget was applied to the *anterior* surface of *both* ventricles a dextrocardiogram was recorded in lead 1 and a laevocardiogram in lead 3 With such treatment only the posterior surfaces were as sumed to be the source of action potentials and it was concluded that the dextrocardiogram in

lead 1 must be derived from the posterior surface of the right ventricle (called posterior dextrocardiogram) and equally the laevocardiogram in lead 3 must have been produced by the posterior surface of the left ventricle (posterior laevocardiogram) If on the other hand the *posterior* surface of *both* ventricles was treated with a KCl pledget a laevocardiogram was recorded in lead 1 and a dextrocardiogram in lead 3 The inference was that the laevocardiogram in lead 1 must be an anterior laevocardiogram—that is arising in the anterior surface of the left ventricle—and the dextrocardiogram in lead 3 must be an anterior dextro cardiogram Therefore lead 1 was believed to record the algebraic summation of the anterior laevocardiogram and the posterior dextrocardiogram lead 3 that of the anterior dextrocardiogram and the posterior laevocardiogram Lead 2 was said to record from the whole heart (Hoff Nahum and Kaufman 1941)

We cannot accept these interpretations as it is certain that the surface areas of the heart are not the only portions which contribute to the electrocardiogram It is the same electrical event which we record in all three leads at any given moment

Nahum Hoff *et al* concluded further that extrasystoles arising in the anterior or posterior septal regions and activating the anterior or posterior surfaces respectively of both ventricles in advance of the opposite surface should have a predictable configuration in the electrocardiogram For example an extrasystole originating from or near the anterior septum should reveal activation of the *anterior* surface of the *left* ventricle in advance of its posterior surface (that is anterior laevocardiogram downward deflection in lead 1) and also activation of the *anterior* surface of the *right* ventricle in advance of its posterior surface (that is anterior dextrocardiogram upright deflection in lead 3) Similarly extrasystoles arising from or near the posterior septum and activating the posterior surfaces of both ventricles in advance of their anterior ones should yield upright deflection in lead 1 (posterior dextrocardiogram) and downward deflections in lead 3 (posterior laevocardiogram) These predictions were found to be correct in experiments on six dogs (Nahum Hoff and Kaufman 1941b) It will be noted that tracings obtained with preceding activation of the anterior surface of both ventricles resemble those of right axis deviation and right bundle branch block (new terminology) those resulting from the preceding activation of the posterior surfaces of both ventricles left axis deviation and left bundle branch block All these tracings were of course discordant Similarly concordant records with upright deflections in leads 1 and 3 were interpreted as indicating that the major portion of the right ventricle is activated before the left one and concordant tracings with downward deflections in leads 1 and 3 preceding activation of the major portion of the left ventricle before the right

A more detailed investigation of the electrocardiographic features of extrasystoles elicited in various parts of the two ventricles showed that right ventricular ones showed downward deflections in certain leads (except those from an area equidistant from all points along the septum termed centre of the ventricle which yielded upright deflections in all three leads) Those downward deflections were shown to arise from excitation of the contra lateral—left—ventricle Conversely left ventricular extrasystoles yielded downward deflections in all leads only if they originated from a restricted area in the centre of the left ventricle upward deflections produced in certain leads by left ventricular extrasystoles arising in other portions of the left ventricle were shown to result from stimulation of the right—contralateral—ventricle (*see also* above in this chapter p 390) (Nahum Hoff and Kaufman 1942)

A similar mechanism was found to be responsible for some differences in the appearance of endocardial and epicardial extrasystoles elicited from closely corresponding points of the heart That these two kinds of premature beats yielded identical deflections in the electro cardiogram had previously been reported by Marcu (1936) Loukomski and Guinodman (1937) and Van Bogaert (1937) but had not attracted much attention Hoff and Nahum

(1943) confirmed this and realized the great importance which this observation has in regard to the interpretation of the genesis of the various deflections in the electrocardiogram (*see* below) They also found two areas in the heart (one in the anterior left and the other in the posterior right ventricle) where epi and endocardial extrasystoles showed different shapes in the electrocardiogram and here again they explained such differences as being due to excitation of the contralateral ventricle

It was then considered possible that chest leads might be more sensitive to detect differences in endo and epicardial extrasystoles Epicardial extrasystoles and their exact endocardial counterparts were therefore studied in seven dogs by a transthoracic lead lead IVR IVF and unipolar (Wilson) lead V The position of the stimulating electrodes was carefully arranged in some experiments they were perfectly centred in line between the transthoracic leads or placed directly beneath the exploring chest electrode in others they were deliberately placed out of alignment either the exploring chest electrode remained in position over the right or left apex and the position of the stimulating electrodes was altered or the precordial electrode was shifted whilst the stimulating electrodes remained in position With the stimulating electrodes in line with the transthoracic lead or immediately beneath the exploring chest electrode no differences between endo and epicardial extrasystoles were found both showed downward (QS) deflections that is negativity beneath the exploring chest electrode When the stimulating electrodes were not in alignment with the transthoracic lead or not beneath the exploring chest electrode various kinds of differences between endo and epicardial extrasystoles were recorded No potentials which must accompany the outward passage of an impulse from endocardium to epicardium were recorded The optimum conditions in which such potentials could be revealed would be those in which the stimulating electrodes were directly in line with the transthoracic lead or directly beneath the exploring chest electrode and these were precisely the conditions in which no differences between endo and epicardial extrasystoles were encountered (Nahum and Hoff 1946)

This observation conflicts with that of Lewis (1922) which had been of such great importance for our views regarding the mechanism of origin of the deflections in the electrocardiogram Using a transthoracic lead in experiments on dogs Lewis stimulated the endocardial and immediately overlying epicardial surface of the right ventricle With forced beats from the endocardium the deflections started with a small downward wave whereas with epicardial extrasystoles the small first wave was directed upwards From this observation Lewis developed his theory of limited potential differences By this is meant that the ventricle should be considered to be composed of a great number of small units and that it is the direction of successive activation of such muscle units which governs the deflection in the electrocardiogram Lewis expressly refuted the view that the position of the activated muscle relative to the rest of the ventricle influenced the electric record

By this time certain factors responsible for disagreement in the past had become apparent of which Nahum and Hoff considered three as the most important (Nahum and Hoff 1945)

1 *Failure to provide for normal conduction from the heart to distant leads* This factor tends to become operative in experiments on animals with widely opened thorax and on human beings with exposed hearts as already stressed by Storm

2 *Preoccupation with the site of origin to the neglect of the sequence of excitation of adjacent and distant regions of the heart* The attempted interpretation of extrasystoles as arising in the right or the left ventricle failed to consider those ectopic beats which originated at or near a septum and thence spread simultaneously to adjacent portions of both ventricles before reaching the more distant parts of the ventricle in which they had arisen This factor accounts for some of the exceptions which were mentioned earlier in this chapter Basing their classification on investigations discussed above (p 390 Nahum Hoff

and Kaufman 1941a Hoff Nahum and Kaufman 1941) Nahum and Hoff recognized four basic patterns which included concordant as well as discordant tracings namely

(1) right lateral concordant main initial deflection upward in all limb leads from the base of the right ventricle to within a few mm of the septum at the apex
(2) left lateral concordant main initial deflection downward in all limb leads from the left lateral margin of the heart including the apex to within about 5 mm of the septum
(3) anterior septal discordant main initial deflection downward in lead 1 upward in 3 from a zone not more than 0 5–2 cm of the apex
(4) posterior septal discordant main initial deflection upward in lead 1 downward in 3 from a zone 0 5–1 cm wide extending from the apex (or a few mm anterior to it) to the base

In all types the T waves were directed opposite to the direction of the main initial deflections In terms of excitation of the various parts of the heart these four basic patterns were interpreted thus

(1) right lateral pattern anterior and posterior surface of the right ventricle activated in advance of the counterparts of the left ventricle origin of extrasystole in the centre of the right ventricle (that is equidistant from the septum)
(2) left lateral pattern anterior and posterior surface of the left ventricle activated in advance of the counterparts of the right ventricle origin of extrasystole in the centre of the left ventricle
(3) anterior septal pattern anterior left ventricle excited in advance of posterior right and anterior right ventricle excited in advance of posterior left ventricle origin of extrasystole at or near the anterior septum
(4) posterior septal pattern posterior surfaces of the two ventricles excited in advance of their anterior surfaces origin of extrasystole at or near the posterior septum

(For the detailed reasoning *see* the original paper)

3 *Inferences from experiments on bundle branch block regarding the site of origin of extrasystoles* Some of the difficulties created by such inferences became apparent in earlier parts of this chapter Barker and collaborators had pointed out that stimulation of all points on the right or the left ventricle does not necessarily yield complexes in the electrocardiogram which closely resemble in all leads those produced by cutting the bundle branch of the contralateral ventricle Nahum and Hoff strongly emphasized this point In bundle branch block the whole of one ventricle is activated in the normal sequence while the opposite ventricle is stimulated from the contiguous borders of the normally activated ventricle

This does not imply that the whole of the normally stimulated ventricle is necessarily activated in advance of the other They give as an example the early activation of the region at the anterior septum in the normal heart of the dog and in that with right bundle branch block It could easily be imagined that in right bundle branch block this portion of the heart is still the earliest to be activated and that adjacent regions of the right ventricle are still activated earlier than some parts of the left ventricle One is certainly not justified to conclude that the conditions governing the sequence of activation are identical in bundle branch block and in extrasystoles originating in the contralateral ventricle

At this stage of the investigations of Nahum Hoff and collaborators it had become evident that their conception conflicted with the dipole theory based on the work of Craib Lewis Wilson and their collaborators In the present context the relevant point of this theory is that in unipolar leads the direction of the deflections is entirely due to the direction of the spread of the excitation relative to the exploring electrode and that more distant parts of the heart contribute only to a small extent

This view cannot be reconciled with the observation of Nahum and Hoff discussed

above that extrasystoles from the epicardium and a point immediately subjacent on the endocardium are virtually indistinguishable in the electrocardiogram On the contrary these workers claim that excitation and recovery on the surface are the factors which determine the electrocardiogram Moreover it was found that all experimental procedures which modify the several components of the normal ventricular complex of an electrocardiogram in a special way produce similar modifications in the same component of a ventricular extrasystole The increase in height of the R wave by cooling the left or warming the right ventricle applying equally to extrasystoles and normal complexes and the identical mode of origin and significance of Q waves in ventricular extrasystoles and normal beats (Hoff Nahum and Kaufman 1942) may be quoted as two of several instances (For others *see* Nahum and Hoff 1945 p 548)

This led Nahum and Hoff to the conception of the zonal interference theory according to which the electrocardiogram of unipolar leads is the result of only two opposing forces the excitation of a proximal region that is at or near or facing the exploring electrode producing a downward deflection (negativity of the exploring electrode) and that of a distal region resulting in an upward deflection the two zones being separated by an intermediate zone These deflections are stated to be independent of the pathway by which the excitation arrives

This conception was developed in regard to unipolar limb leads and the praecordial electrocardiogram of the dog

Findings regarding unipolar limb leads may be illustrated by lead VR obtained by an exploring electrode on the right forelimb which was paired with a central terminal from right and left forelimbs and left hind limb In order to delimit the proximal distal and intermediate zones several methods were employed By momentarily applying positive or negative electrical potentials of low voltage to various parts of the heart the areas from which downward or upright deflections were obtained were mapped out The direction of the main initial deflection of extrasystoles produced by break shocks in various parts of the heart was charted and similarly the effect upon the S-T segment of localized surface injury from application of M 5 KCl solution or superficial cautery These methods gave consistent results in delimiting a proximal zone facing the electrode and a distal zone facing away from the electrode which were separated by an intermediate zone Extrasystoles originating in the proximal zone showed the main deflection directed downward (QS complex) those arising in the distal zone produced an upward deflection (R wave) those from the intermediate zone an rS or qRs complex Similarly elevation of the S-T segment as a result of local injury localized the site of injury in the proximal depression of S T in the distal zone Impressed negative potentials on the right ventricle caused a negative on the left ventricle an upward deflection By these methods the proximal distal and intermediate zones were mapped out in detail for leads VR VL and VF (Nahum Chernoff and Kaufman 1948a)

Similar investigations were carried out regarding the mode of origin of the T wave (Hoff and Nahum 1945)

As already mentioned this group of workers endeavoured to show that in each of the three unipolar limb leads a proximal distal and intermediate zone specific for each of these leads could be delimited Extrasystoles originating in the proximal zone were characterized in the particular lead by an initial downward those from the distal zone by an upward deflection These zones were however comparatively large Delimitation of the site of origin within a smaller area was attempted by simultaneously recording two or three unipolar extremity leads Since the proximal distal and intermediate zones of these three leads overlap such simultaneous recording would delimit the site of origin of extrasystoles within a far narrower area This may be illustrated by Fig 184 taken from Nahum Chernoff and Kaufman 1948b For example an extrasystole showing a downward initial deflection in

leads VR and VL and an upward deflection in lead VF can be assumed to originate in a zone which is proximal in leads VR and VL and distal in lead VF and therefore would be situated in the basal part of the anterior surface of the right ventricle (marked PPD in the diagram) In a similar way an extrasystole showing an upward deflection in leads VR and VL and a downward one in lead VF was assumed to have arisen in a zone which is distal

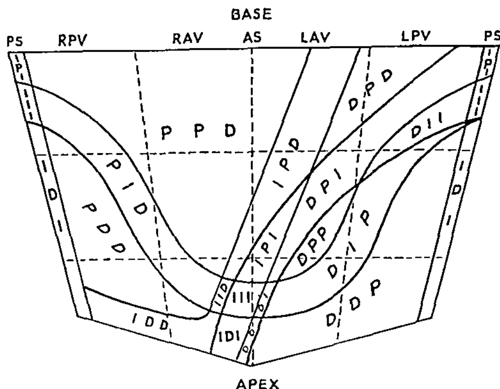


FIG 184—Schematic drawing of ventricular surface of dog heart showing overlapping of the proximal intermediate and distal zones of leads VR VL and VF PS posterior septum RPV right posterior ventricle RAV right anterior ventricle AS anterior septum LAV left anterior ventricle LPV left posterior ventricle P proximal zone I intermediate zone D distal zone The various areas are labelled in the diagram according to their zonal representation in leads VR VL and VF The first of the three letters which label each of the areas represent the zone of lead VR the second letter the zone of lead VL and the third letter the zone of lead VF For further explanation see text From NAHUM CHERNOFF and KAUFMAN 1948 b *Amer J Physiol*

in leads VR and VL and proximal in lead VF which localizes its origin in the apical portion of the anterior surface and the apical and middle portions of the posterior surface of the left ventricle designated DDP

This group of workers also applied their methods to a more detailed analysis of standard (bipolar) limb leads

An isoelectric interval in the record of a bipolar lead may be due to any one of three possibilities

(1) negative potentials of equal magnitude at both extremities

(2) positive potentials of equal magnitude at both extremities
(3) zero potentials at both extremities (Nahum Chernoff and Kaufman 1948b)

By simultaneously recording one bipolar and two unipolar limb leads the authors considered possible

1 to determine which of the combinations of potentials of the two individual extremities resulted in a bipolar limb lead in an upward or downward deflection or an isoelectric interval and

2 to delimit within a narrower area the site of origin of extrasystoles yielding upright or downward deflections in lead 1 or 3 than had been possible by the limb leads alone

In the context of this book the second aspect is the more relevant

In earlier investigations (Nahum Hoff and Kaufman 1941a Hoff Nahum and Kaufman 1941 Nahum and Hoff 1945) discussed above these workers recognized four basic patterns of ventricular extrasystoles according to the direction of the deflection in the bipolar limb leads each pattern indicating the site of origin within a comparatively large area of the heart By analysing the mechanism of these deflections in the limb leads into the simultaneously recorded deflections in each of the two component unipolar leads the authors attempted to delimit the area of depolarization—and in the case of extrasystoles this gives an indication of the site of their origin—within a considerably smaller portion of the heart Lead 1 was studied as a derivation from an analysis of simultaneously recorded leads VR and VL lead 3 of leads VL and VF

This may be illustrated in respect of lead 1 From earlier investigations the same group of workers had concluded that in this lead an upright deflection resulted mainly from depolarization of the posterior right ventricle and a downward deflection from that of the anterior left ventricle Further investigations with simultaneously recorded unipolar limb leads revealed that the greatest upward deflection occurred as a result of depolarization of the mid third of the posterior right ventricle The reason was found to be that extrasystoles precipitated from this area yielded opposite deflections in the unipolar leads VR and VL (downward in the former upright in the latter) and since the right forelimb was initially negative relative to the left one lead 1 showed a large upward deflection Conversely the largest downward deflections in lead 1 were found when the mid third of the anterior left ventricle was depolarized extrasystoles elicited in this area produced opposite deflections in leads VR and VL (upright in the former downward in the latter) and since the right forelimb was initially positive relative to the left one such extrasystoles yielded large downward deflections in lead 1

The inclusion in these studies of those parts of the heart the depolarization of which did not manifest itself by an appreciable deflection in lead 1 made it possible to analyse which of the three possibilities mentioned above resulted in isoelectricity Extrasystoles elicited from one of these portions namely the lower third of the posterior left ventricle showed an interesting feature during the first 0 04 second an isoelectric interval was recorded in lead 1 although the rapid downward deflection in lead 3 during that interval indicated that parts of the heart were being activated during that time The explanation for this isoelectric interval in lead 1 was revealed by leads VR and VL in both of which the deflection during that 0 04 second was ascending with the same gradient since at both forelimbs potentials of the same magnitude and of the same electrical sign developed at the same speed no potential differences between the two forelimbs were recorded in lead 1

In a similar way lead 3 was analysed from simultaneously recorded leads VF and VL with regard to regions of the heart the depolarization of which yielded maximal less than maximal and no deflections in this limb lead In both leads 1 and 3 the effect upon the T wave of accelerating or decelerating repolarization by warming or cooling various portions of the heart was also investigated

These extensive investigations seemed to their authors to be in agreement with their earlier findings that lead 1 records the algebraic summation of potentials derived mainly from depolarization of the posterior right and anterior left ventricles whereas that of the anterior right and posterior left ventricles was not represented in this lead that lead 3 records the algebraic summation of potentials derived mainly from depolarization of the anterior right and posterior left ventricles whereas that of the anterior left and posterior right ventricles was not represented in this lead By this method delimitation of the area of depolarization within a more specific and circumscribed area of the heart was claimed and a basis for the presence or absence of electrical representation of the various regions of the heart in leads 1 and 3 was thought to have been established

In a similar way proximal distal and intermediate zones were mapped out for praecordial leads (Nahum and Hoff 1948) The exploring chest electrode was placed either opposite the left apex on the left side of the chest or the right apex on the right side of the chest CF CR and CV leads were employed and the delimitation of the zones investigated by three methods

(1) influence on the S T segment of localized application of 0 1 M KCl solution

(2) influence upon the T wave of local warming and cooling

and

(3) the shape of extrasystoles elicited from various parts of the heart

These three methods gave consistent results As far as extrasystoles are concerned those precipitated in the proximal zone yielded simple QS deflections those arising in the distant zone R waves and those elicited in the intermediate zone showed QRS patterns with the R wave becoming more prominent as the point of stimulation approached the distal and the S waves as it approached the proximal zone In all leads studied the method of extrasystoles permitted a more exact definition of the various zones than did the effect of warming or cooling or localized surface injury The three leads employed yielded essentially the same information but leads CR and CF were slightly superior to CV regarding sharpness of delimitation of the various zones With each position of the chest electrode the proximal zone always included at least the apex of the ventricle corresponding to the side of the chest lead selected while the distal zone always included some portions of the base of the heart In other words the chest leads always included an element of base apex interference Figs 185 and 186 taken from their paper show the position size and shape of the three zones

All such analyses are based on the zonal interference theory of this school of workers This conflicts with Lewis s theory of limited potential differences which as further developed by Wilson and his collaborators has been the universally accepted basis of the genesis of the electrocardiogram The zonal interference theory itself is based on the essential identity in the appearance of extrasystoles elicited from closely corresponding points on the endo and epicardium This experimental basis of Nahum and Hoff s views has not been confirmed so far On the contrary Attyah found in dogs that electrical stimulation of the endocardial surface of the free wall of the right ventricle consistently yielded initial positivity on the superjacent epicardial electrode (which was paired with Wilson s central terminal) This is in accordance with the dipole theory and at variance with Nahum and Hoff s findings On the other hand Durant and Oppenheimer studying in dogs extrasystoles elicited mechanically found a small area producing initial negativity in direct leads from the site of stimulation They also obtained a small point of initial negativity in spontaneous systoles and found that the zonal interference theory best explained their experimental results which would be difficult to understand on the basis of the dipole theory

A more serious fundamental objection to the zonal interference theory is the fact that it conflicts with the results of vectoranalysis and vectorcardiography These methods have

shown that *all* parts of the heart contribute to the electrocardiogram at any moment in any lead They have also demonstrated that the degree of proximity of an electrode to a given region of the heart influences the contour of the record to a far smaller extent than previously assumed and have cast doubt on the possibility of identifying an intrinsic deflection as indicating the arrival of the excitation beneath the exploring electrode Moreover tracings obtained from diametrically opposite points of the chest yield deflections which are mirror images of one another For further particulars of these investigations the reader is referred to the monographs of Duchosal and Sulzer and of Grant and Estes

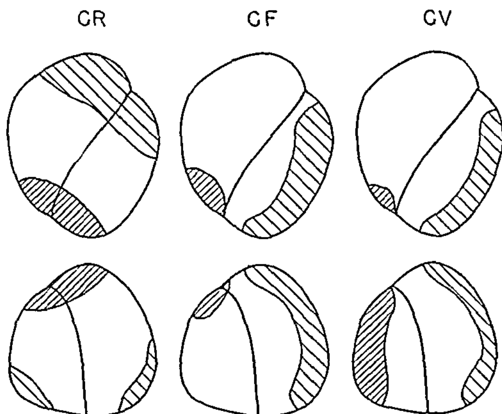


FIG 185 —Summary of the proximal and distal zones of the dog heart when the lead is taken with the exploring electrode placed over the right apex CR CF and CV leads *Above* ventral surface of the heart apex down *below* dorsal surface of the heart apex up *Fine shading* proximal zones *coarse shading* distal zones For further explanation see text From NAHUM and HOFF 1948 *Amer J Physiol*

The relevant fact in the present context is that because of these findings grave doubts exist about the validity of the conclusions which Nahum Hoff and their co workers have drawn from their investigations and in particular about that of the zonal interference theory The outcome of further investigations has to be awaited before a definite opinion can be formed

Oesophageal Leads

The use of oesophageal leads has not proved very helpful in the determination of the site of origin of ventricular extrasystoles (Brown Spuhler Wunsche 1948) It is of interest that

the oesophageal pulsations (that is pulsations of auricle and ventricle transmitted to the oesophagus) were used for the analysis of extrasystoles as early as 1907 (Rautenberg)

Endocardial Leads

Of late studies on intracavity potentials have supplemented these observations but as yet have not clarified the problems of localizing the site of origin of ventricular extrasystoles

Extrasystoles originating in the right ventricle yield large QS deflections in the electro cardiogram from the right ventricle in man (Battro and Bidoggia 1947 Sodi Pallares *et al*

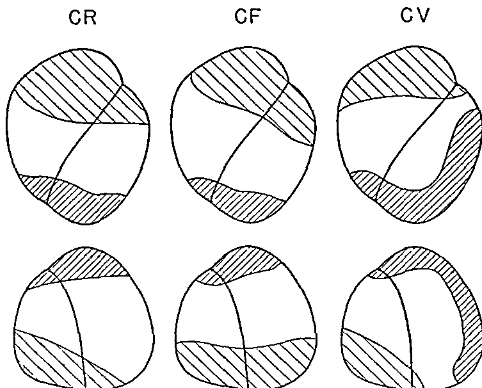


Fig 186 —Summary of proximal and distal zones of the heart when the lead is taken with the exploring electrode over the left apex *Fine shading* proximal zones *coarse shading* distal zones For further explanation see text From Nahum and Hoff 1948 *Amer J Physiol*

1947 Battro 1948 Levine *et al* 1949) and in dogs (Sodi Pallares *et al*) whereas left ventricular extrasystoles give RS deflections (Hecht 1946 Battro and Bidoggia) The elec troendocardiogram from the right ventricle of right ventricular extrasystoles resembles in its deep QS deflections those of left bundle branch block and that of left ventricular extra systoles in its RS configuration that of right bundle branch block Also the electroendo cardiogram of the left ventricle in left bundle branch block resembles in its essential features that from the right ventricle in right bundle branch block The data regarding intracavity potentials which are so far available are inadequate for drawing more detailed conclusions as to the underlying mechanism Apart from having been established as yet on a small number of cases the tracings reproduced in the few publications are not strictly comparable

because of technical reasons (for instance wide exposure of the heart and the use of only one limb for the indifferent electrode Sodi Pallares) With these reservations it may be said that most findings are in accordance with the dipole theory and Wilson s views based thereon but the intracavity potentials recorded of extrasystoles would also be in accordance with the conception of Nahum and Hoff In most observations made on man these refer to right ventricular extrasystoles and there are good reasons for assuming that they were produced by the exploring intracavity electrode mainly from the point where it was in intermittent contact with the endocardial surface of the right ventricle (Levine *et al*) In this event the intracardiac electrode being at the same time the (mechanically) stimulating and the recording electrode the deep QS deflections being obtained from the very site of stimulation would accord well with Nahum and Hoff s analogous findings on extrasystoles elicited in the proximal zone but would accord equally well with the dipole theory The presence of a high R wave in the right ventricular electroendocardiogram in cases of left ventricular extrasystoles (Hecht Battro and Bidoggia) could be interpreted as being due to the origin of the extrasystoles in the distal area The close resemblance of supraventricular beats in the right ventricular electroendocardiogram and in a simultaneously recorded praecordial lead obtained from a point immediately above the endocardial-electrode (Kossmann *et al* 1948 Fig 11) tends to support Nahum and Hoff s views However since the exact position within the right ventricle of the endocardial electrode cannot be ascertained and the praecordial lead can be considered to be only an approximation to a direct epicardial lead further investigations have to be awaited until more definite conclusions can be drawn

Vectorcardiography

The possible value of vector diagrams for the determination of the site of origin of extrasystoles was already pointed out by Mann whose Monocardiogram is one type of frontal vectorcardiogram (Mann 1931 1938) also by Schellong (1939) Another early attempt along similar lines (Hollmann and Guckes 1939) based on a Triogramm (a vector recorded by three leads by means of a specially adapted Braun s tube) proved unsatisfactory regarding delimitation of such focus of origin in any definite portion of the heart With the more recent development of vectorcardiographic methods this problem was considered by several authors Duchosal and Sulzer pointed out that the vectorcardiograms of ventricular extrasystoles were very different from those of bundle branch block (p 153) The most comprehensive application so far of vector methods to this problem is that of Donzelot Milanovich and Kaufmann It is claimed that the kind of vectorcardiography and electrovectorcardiography as developed by this group of workers makes the location of ventricular extrasystoles a matter d une etrange simplicité Vectograms are recorded by a cathode ray tube in one of three planes from two unipolar leads as follows frontal (V 6 V F) horizontal (V 2 V 6) and sagittal (V 2 V F) In the frontal vectogram origin of the extrasystole in the right or left and upper or lower part of the heart can be determined by the inclination of the QRS loop the horizontal vectogram provides additional information as to anterior or posterior location of the focus If vectograms in these two planes are available a ventricular extrasystole can be classified in a more detailed way for example as left posterior and superior or as right anterior and inferior and from such information the part of the ventricle can be deduced where the ectopic beat arose In support of this view these authors point out (a) that if the electrocardiograms in the frontal and horizontal planes are constructed from the vectorial loops the tracings point to the same diagnosis as the vectogram and (b) that these interpretations are in accordance with findings obtained with artificially produced ectopic beats in the exposed hearts of animals and man While we cannot claim any personal experience in vectorcardiography we should like to state by way of general comment that both these

arguments seem to us unconvincing the first because the criteria for determining the site of origin of ventricular extrasystoles in any scalar lead are still controversial the features of such records depending also on factors other than the site of origin of the ectopic beat the second because results obtained in artificially elicited ectopic beats in such conditions are applicable to the localization of the site of origin of spontaneous extrasystoles in man only with the greatest reserve because of the modifying influence of many factors (for example position of the heart exposure of the organ electrical properties of surrounding media manner of spread) Even if the direction of the loops in vectograms in various planes made possible an exact spatial localization of the focus its location in a definite portion of the heart would still not have been established this would only be possible if the anatomical position of the heart in relation to the three axes could accurately be determined from the vectograms

It seems to us that recent developments in vectorcardiography are promising in furthering the elucidation of this problem but that the present stage is only a beginning as Donzelot *et al* themselves say L étude des extrasystoles ventriculaires est d ailleurs loin d etre close

Clinical Applications

Compared with the great physiological interest of these more recent investigations their clinical importance is as yet small One clinical application seems to be the determination of the site of myocardial infarction in cases of coronary occlusion for which some experi mental basis is already laid The occurrence of ventricular extrasystoles in cases of myo cardial infarction is of course frequently observed and there are good reasons to assume that they originate in the partially ischaemic border zone between the infarcted area and normal muscle (Harris and Rojas 1943) In view of this Hoff and Nahum (1945) correlated in experiments on thirteen dogs the shape in the electrocardiogram of spontaneous ventricular extrasystoles and the direction of the displacement of the S T intervals in leads 1 and 3 resulting from local myocardial ischaemia which was produced in four different areas of the heart by ligating branches of the coronary arteries namely in the right lateral left lateral anterior and posterior portions of the myocardium In all cases complete agreement was found between

1 the position and course of the occluded artery
2 the region of the heart which became cyanotic
3 the pattern of the S T displacement and
4 the configuration of the extrasystoles in the two leads

The appearance of extrasystoles in the standard leads may thus be helpful to determine the site of myocardial infarction This method might lend itself to be further developed by being extended to chest and unipolar limb leads and eventually to be applied to the localiz ation of myocardial infarcts in clinical cases but we are aware of considerable difficulties which are likely to arise

AURICULAR EXTRASYSTOLES

Compared with the amount of work and thought lavished on the localization of the site of origin of *ventricular* extrasystoles that of *auricular* ones has attracted far less attention This is understandable for various reasons the greater frequency of ventricular ectopic beats the larger size and the more conspicuous variations in shape of their deflections in the electrocardiogram the greater mass of ventricular musculature the presence of a well defined conducting system in the ventricles the recognized great clinical importance of multiform ventricular extrasystoles and the ominous significance of ventricular fibrillation of which these may be the precursors all these factors make the study of the site of impulse

formation of ventricular extrasystoles appear more important and promising than that of their auricular counterparts All the same a more intimate knowledge of the site of impulse formation (and mode of spread) of auricular extrasystoles may in future well become of greater physiological and clinical importance than may be obvious at present For quite apart from any intrinsic interest of this problem auricular extrasystoles are so often the precursors of other disorders of auricular rhythm such as auricular fibrillation flutter and paroxysmal tachycardia that any such increase in knowledge appertaining to auricular ectopic beats may in its train bring about a better understanding of auricular arrhythmias generally

It is to be expected that the nearer to the normal pacemaker an auricular extrasystole originates the more closely does its P wave resemble that of the sino auricular beats This was established by Lewis in 1910 in the early days of electrocardiography In experiments on dogs he found that in lead 2 auricular premature beats elicited by induction shocks showed normal P waves only if they were produced from points in close proximity to the sino auricular node that is from the superior vena cava—auricular junction An instructive tracing is to be found in Lewis s monograph (1925c) Those from the inlet of the inferior vena cava showed small polyphasic P waves with a tendency to isoelectricity (*see also* Lewis and White 1914 Figs 2 and 5) those from the inlet of the pulmonary veins usually yielded P waves which started with an inverted phase Those from the interior of the right auricle namely the coronary sinus showed also inverted P waves and in one such instance the P R interval was shortened and the origin of the premature beat was considered to be very near the A V node Upright P waves but differing in outline from normal ones were found in extrasystoles originating in the base and tip of the right auricular appendix In the same paper Lewis applied these experimental findings to the interpretation of human curves Using lead 2 he distinguished three main types of auricular extrasystoles in man

(1) those with upright P waves in which cases the ectopic beat was considered to originate in the upper regions of the auricle in the neighbourhood of the S A node
(2) with inverted P waves these were taken to indicate origin in the lowest regions of auricular musculature namely in the neighbourhood of the A V node or in the absence of a shortened P R interval possibly in the region of the pulmonary veins
(3) those with isoelectric or diphasic P waves signifying impulse formation in the middle part of the auricle the neighbourhood of the inferior vena cava or pulmonary veins or appendix of the left auricle

Lewis concluded An absolute localization is of necessity impossible at the present stage of the enquiry nevertheless localization is obviously possible within certain limits (p 34) And this conclusion still holds good after about forty years While in many other fields of electrocardiography great progress has been made during that period our knowledge in this particular question has not materially advanced The realization of the importance of intra auricular disturbances of conduction in relation to the shape of P waves (Scherf and Shookhoff 1926 Rothberger and Scherf 1927) has brought into relief an important difficulty in the elucidation of this problem If abnormal conduction in the auricles can alter the shape of P waves to such an extent that inverted P waves can in certain circumstances be observed in cases of unquestionable sinus rhythm and A V beats can be associated with upright P waves it is no longer possible unreservedly to consider the shape of P waves as indicative of the site of impulse formation within the auricles This consideration alone also invalidates Schellong s attempt dubious in many other respects at localization of auricular beats from the shape of P waves in three special leads each recorded from two points on the anterior chest wall the lines of the leads all passing through the centre of the auricles projected on to the anterior chest wall (Schellong 1926)

It is certain however that auricular extrasystoles originating in the lower parts of the auricles near the A V node show a very low positive P wave in lead 1 and deep sharply inverted P waves in leads 2 and 3 This pattern of P waves in the standard leads is typically seen in A V rhythm

In the augmented unipolar extremity (aV) leads extrasystoles originating in the upper parts of the auricles near the sinus node show inverted P waves in lead aVR and upright P waves in lead aVF With a focus of origin of the extrasystoles in the area near the auricular part of the A V node the P waves are upright in aVR and inverted in aVF (*see* Fig 58)

Oesophageal leads in which the exploring electrode is in close proximity to the left auricle lend themselves to the study of this problem Brown (1936) drew attention to the importance of the moment of onset of the intrinsic deflection of the extrasystole which indicates the moment of activation of the area beneath the exploring electrode If in the oesophageal lead the extrasystole starts immediately with the intrinsic deflection the conclusion seemed warranted that the extrasystole originated almost exactly beneath the oesophageal electrode In one such instance (*see* his Fig 12 p 26) the total duration of the P wave of the premature beat was lengthened to 0 1367 second from the 0 0849 second of the normal P waves Brown interpreted this as indicating a different path of spread through the auricles of the ectopic beat A similar observation is contained in a paper by Wunsche (1945) Using an oesophageal lead in which the exploring electrode was paired with a central terminal (Wilson) he obtained upright P waves of normal beats whereas those assumed to have originated in the left auricle yielded inverted ones their downstroke started immediately This intrinsic deflection was often split this was attributed to a different intra auricular spread of the ectopic impulse and the slight lengthening of the intra auricular conduction time supported this explanation In view of the grave doubts which have recently been cast on the possibility of identifying an intrinsic deflection the interpretation of these investigations has to be accepted with great reserve *see also* p 377 (Spread of the Excitation) *also* Brown (record 4 of his Fig 24 p 41) Both Brown s and Wunsche s observations illustrate the close relationship between site of impulse formation and abnormal spread through the auricles of premature auricular beats as revealed in oesophageal leads

Deglaude and Laubry (1939) mention that the difference in shape in the oesophageal electrocardiogram between the normal P waves and those of auricular extrasystoles makes it sometimes possible to determine their site of origin but do not give any particulars

If praecordial leads are employed for such investigations the choice of the indifferent electrode is of great importance A central terminal is far preferable to either CR or CF leads since in the latter the potential differences of the indifferent electrode exert a profound influence on the shape of the P waves (Brown and Ellis 1947)

The more recently developed technique of the recording of intracavity potentials by means of cardiac catheterization has yielded some further information about this problem without as yet contributing much to the determination of the site of origin of spontaneous auricular extrasystoles For just as with ventricular extrasystoles there is every reason to assume that auricular ones occurring during catheterization are elicited by the exploring electrode by means of mechanical stimulation of the endocardial surface of the (right) auricle Auricular premature beats occurring in such circumstances have been described by Hecht (1946) Battro and Bidoggia (1947) and Levine Hellems Wittenborg and Dexter (1949) Such ectopic beats usually appearing singly occur far less frequently than ventricular ones The reason is believed to be that the intracardiac electrode is more prone to remain in the atrium in midstream and therefore is not usually placed in a position favourable for eliciting extrasystoles by being in intermittent contact with the wall of the chamber (*see also* section on Catheterization) Auricular premature beats were found by Levine *et al* in four out of twenty one studied subjects Usually the P waves of the extrasystoles started with a sharp downward deflection interpreted according to the dipole theory

as being the intrinsic deflection and indicating that at that time the impulse travelled away from the electrode. The inference is that the contact of the tip of the electrode actually elicited the ectopic beat. In one instance it was found that while in the intracavity lead the P waves of the ectopic beats differed somewhat from that of normal beats such differences were more pronounced in lead V 2 simultaneously recorded; the assumption seemed justified that in this case the praecordial electrode was nearer to the site of ectopic impulse formation than the intracavity one. In only one case were four auricular extrasystoles observed in succession all showing sharply inverted P waves which however differed in shape somewhat from one another. Simultaneously recorded intracavity and oesophageal electrocardiograms both electrodes being inserted at the same vertical distance from the suprasternal notch showed that the intrinsic deflection of normal beats occurred in the oesophageal electrocardiogram 0 05-0 07 second later than in the right auricular electro endocardiogram. In the case of auricular extrasystoles this delay was increased to 0 11 to 0 13 second. This is interpreted as indicating that the impulse arising at the ectopic site at or near the tip of the intra auricular electrode pursued a longer course to the point in the left atrium tapped by the oesophageal electrode than impulses arising in the normal pace maker (Levine *et al* 1949)

ECTOPIC IMPULSE FORMATION AND SPECIALIZED TISSUE

Another aspect of the problem of localization of the focus of origin of extrasystoles and of ectopic impulses generally is the question whether the origin of such beats is confined to specialized tissue or whether they can also originate in the common myocardium

Although for reasons discussed below in this section the problem has now lost much of its importance it seems desirable to discuss it briefly as it had given rise to considerable *controversy in the past and in its investigation some findings of more general physiological* interest were obtained

The view that ectopic beats can originate only in the specialized tissue was attractive from the start because of the fact that the *normal* impulse originates in such specialized tissue. Some early observations seemed to support this view. Of these Marchand s findings may be mentioned that one make shock applied to the A V border of a frog s heart produced several contractions. Gaskell s analogous findings regarding a mechanical stimulus applied to this region and Tigerstedt and Strömberg s similar observations made on the sinus of the frog s heart though such repetitive response to one stimulus could be obtained from various portions of the heart (*see* chapter on Mechanism). However the assumption that the specialized tissue is the only one which may give rise to ectopic beats was supported by Mackenzie by Lewis and Silberberg and by Koch. Ishihara and Nomura found automatic impulse formation in the spurious tendons of the dog s heart while it was absent in the common muscle fibres. Lewis in the last edition of his classical monograph stated (1925) There is little to suggest that extrasystoles can spring from ventricular muscle as opposed to Purkinje tissue

Even if automatic impulse formation was found in strips of the common myocardium the presence in such strips of specialized fibres could not be excluded. Actually it was found histologically in many of them and spontaneous rhythms were more pronounced in those which contained such fibres (Greene and Siddle). The smallest groups of specialized fibres were found to be capable of initiating spontaneous contractions (Skramlik)

The difference in the effect upon ectopic impulse formation of warming different portions of the heart in dogs sensitized by the systemic application of small doses of barium seemed to support this view. If such small doses of barium were used that no alteration in cardiac rhythm resulted warming by means of a thermode of any part of the *ventricles* elicited ectopic tachycardias originating in the warmed area. Warming of the *auricles* on

the other hand at a distance of the S A and A V nodes failed to precipitate such ectopic arrhythmias The inference was that the ectopic ventricular tachycardias were due to the enhancing effect of warming upon the specialized system (Purkinje ramifications) so that the automaticity of the warmed portions of this system exceeded that of the S A node and thus became the pacemaker In the auricles on the other hand this effect was absent because specialized fibres were absent (Scherf 1927 a and b)

The frequent occurrence of ectopic arrhythmias during catheterization was interpreted as supporting the origin of such ectopic impulses in specialized tissue namely the subendocardial network of Purkinje fibres (Landtman)

Support for the opposite view was not lacking namely that ectopic impulse formation may take place in the common myocardium being independent of specialized tissue Taussig and Meserve found rhythmic stimulus formation in isolated strips of the myocardium and even questioned whether isolated specialized tissue without any common myocardial fibres attached was capable of automatic impulse formation In the hearts of rabbits and guinea pigs Rothberger and Sachs investigated spontaneous impulse formation in isolated strips of the outer wall of the left auricle or of the apex and found it present in seven out of sixty five preparations If aconitine or veratrine was added to the nutrient (Soejima s) solution rhythmic activity was observed in all preparations In these portions of the heart specialized tissue is thought to be absent and in fact Aschoff s histological examination of such strips failed to demonstrate it Rothberger and Sachs concluded that ectopic impulses may be formed independently of specialized tissue Moreover *topical* application of various compounds (sodium chloride barium chloride strophanthin digitalis aconitine veratrine) to any part of the dog s heart *in situ* ventricle or auricle even appendix of the left auricle results in ectopic impulse formation and ectopic tachycardias originating at the site of application These studies are discussed in the appropriate sections of this book (Extrasystoles and Drugs and Electrolytes)

The conclusions drawn from such observations had to be modified in view of the more recent discovery that the ramifications of the specialized system were far more extensive than previously assumed It was found that such fibres contiguous with and structurally alike the subendocardial network extended throughout the myocardium to within a few mm of the epicardial surface The relevant investigations are discussed in the section on Spread of the Excitation (p 374) where it is also pointed out that the histological differentiation between specialized and common myocardial fibres is fraught with difficulties On the other hand none of the various claims to have demonstrated specialized fibres in the auricles have stood the test of more careful histological re examination and none of such fibres could be shown to possess the capacity of automatic impulse formation

The *conclusions* to be drawn from such contradictory findings seem to be that in certain experimental conditions ectopic impulse formation is possible in any part of the heart Whether the presence of specialized tissue is indispensable remains undecided The observation that skeletal muscle may in certain circumstances show rhythmic impulse formation would seem to support the assumption that analogous conditions may prevail also in the common myocardium but the application to cardiac muscle of findings observed in skeletal muscle is not permissible without considerable reserve and such assumption is therefore admittedly only conjectural

SUMMARY

Ventricular Extrasystoles

The determination of the focus of origin of ventricular extrasystoles while until recently considered to have only an academic if any importance has become of increasing

consequence during the last twenty years since such investigations proved to be of considerable moment in connexion with other problems of cardiac physiology and pathology and of late with the interpretation of the electrocardiogram generally

The various stages in the research on this problem can conveniently be divided into four periods

First Period

From the investigations of Kraus and Nicolai starting in 1907 up to those of Rothberger and Winterberg in 1913 and of Lewis in 1916 Much of the work published at this stage is now only of historical interest This applies for instance to the controversy whether the direction of the initial deflections signified a right left ventricular or apical basal origin of the ectopic beat neither of which views has in this form stood the test of time The importance of the lead employed was often not realized although as early as 1908 Einthoven stated that lead 1 distinguished between right and left half of the heart and lead 3 between apical and basal portions upward directed deflections in lead 1 he considered indicative of origin of the ectopic impulse in the right downward ones in the left half of the heart upward and downward directed deflections in lead 3 he assumed to signify basal and apical origin respectively As far as a right left ventricular or apical basal localization can be at all deduced from the direction of the initial deflections in the various limb leads this early view of Einthoven s has been shown to be remarkably correct by subsequent investigations some of them comparatively recent

Second Period

From the investigations of Rothberger and Winterberg in 1913 and those of Lewis in 1916 to those of Barker Macleod and Alexander in 1930 Rothberger and Winterberg concluded from extensive experimental observations that the factor which determined the shape in the electrocardiogram of ventricular ectopic beats was the location of the stimulated point in relation to the point of the specialized conducting system whence the further spread of the excitation took place The work of this period which was to have the most lasting effect was that of Lewis in whose opinion extrasystoles showing downward initial deflections in lead 1 and upright ones in lead 3 arose in the right ventricle whereas left ventricular ones yielded upright initial deflections in lead 1 and downward ones in lead 3 This interpretation prevailed until 1930

Third Period

From 1930 when the observations of Barker Macleod and Alexander on an exposed heart in man threw doubt on Lewis s interpretation to about 1940 when the extensive experimental investigations of Nahum Hoff and collaborators started As a result of direct stimulation of a human heart exposed at operation Barker Macleod and Alexander arrived at the conclusion that Lewis s terminology should be reversed namely that the direction in the various limb leads, which Lewis took to indicate right ventricular actually signified left ventricular origin and vice versa This entailed not only a reversal of the terminology regarding the side of origin of ventricular ectopic beats but also a similar reversal in the interpretation of bundle branch block curves and the necessity of new explanations of right and left ventricular preponderance During the subsequent decade the observations of Barker Macleod and Alexander were confirmed and the reversal of the terminology regarding the interpretation of electrocardiograms in relation to the side of origin of extra systoles and of those of bundle branch block curves was supported by experimental and clinical observations At the same time it was realized that the new terminology was only applicable with certain qualifications The importance of the position of the heart and of the structure of the surrounding tissues was realized as accounting for some of the exceptions

encountered in some instances clinical as well as experimental Other exceptions had not found a satisfactory explanation such as the occasional occurrence of left or right ventricular extrasystoles elicited from portions of the contralateral ventricle The meaning of concordant and discordant tracings was obscure and the applicability of findings ob tained in cases of bundle branch block to those of extrasystoles and vice versa was not entirely clarified

Fourth Period

From 1940 to the present This phase is dominated by the extensive investigations of Nahum Hoff and collaborators Starting from a reinvestigation of the dual nature of the normal electrocardiogram as a resultant of dextro and laevocardiogram these workers by eliminating the surface potentials of known portions of the heart claimed to have established four basic patterns of extrasystoles

(1) right lateral concordant main initial deflection upward in all limb leads origin of extrasystole in the centre of the right ventricle that is equidistant from the septum
(2) left lateral concordant main initial deflection downward in all limb leads origin of extrasystole in the centre of the left ventricle
(3) anterior septal discordant main initial deflection downward in lead 1 upward in lead 3 origin of extrasystole at or near the anterior septum
(4) posterior septal discordant main initial deflection upward in lead 1 downward in lead 3 origin of extrasystole at or near the posterior septum

Certain exceptions were shown to be due to the activation of portions of the contralateral ventricle in advance of the one in which the extrasystole had been elicited The limits within which the findings obtained in cases of bundle branch block were applicable to those of extrasystoles and vice versa became better understood The observation that extra systoles elicited from a point of the epicardium and from one immediately subjacent of the endocardium were indistinguishable in the electrocardiogram was made again (but objec tions to the technique were raised) and its great importance for the interpretation of the electrocardiogram generally was realized For this observation if confirmed is not com patible with the current dipole theory of the electrocardiogram according to which the direction of the spread of the excitation wave in relation to the exploring electrode deter mines the direction of the deflection in the record As a result of further investigations which included the use of chest leads this school of workers developed a new conception of the genesis of deflections in the electrocardiogram termed zonal interference theory According to this the electrocardiogram of unipolar leads is the result of only two opposing forces the excitation of a proximal region that is at or near or facing the exploring elec trode producing a downward deflection (negativity of the exploring electrode) and that of a distal region facing away from the exploring electrode resulting in an upward deflection the two zones being separated by an intermediate zone the deflections in the record were found to be independent of the pathway by which the excitation arrives The proximal distal and intermediate zones were determined for the three unipolar limb and for two uni polar chest leads Since in the three unipolar limb leads these three zones overlap it was attempted by simultaneously recording two or three unipolar limb leads to delimit the site of origin of extrasystoles within a far narrower area than had been possible by using only one unipolar limb lead By simultaneously recording one bipolar and two unipolar limb leads it was attempted to determine the mechanism underlying the appearance of upright or inverted deflections of extrasystoles in a bipolar limb lead as the resultant of the differences of potential of each component unipolar limb electrode and to delimit within a narrower area the site of origin of the ectopic beats than had been possible by standard bipolar limb

leads alone At the present moment it does not seem possible to reconcile the observations of this school of workers with the current theory of the origin of deflections in the electro cardiogram on its part based on a wealth of experimental and clinical observations These investigations are at present not confirmed Moreover vectoranalysis and vectorcardio graphy have demonstrated that *all* parts of the heart contribute to the electrocardiogram at any moment in any lead that regarding the contour of the electrocardiographic record the degree of proximity of the exploring electrode is of far less importance than believed in the past and that our conceptions about the determination of an intrinsic deflection as indi cating the arrival of an excitation beneath the exploring electrode need reconsideration For these reasons grave doubts exist about the validity of the zonal interference theory Any judgment of the significance of these investigations must of necessity be provisional

The results of more recent investigations by means of *oesophageal leads* by *records of intracavity potentials* obtained with cardiac catheterization and by *vectorcardiograms* are briefly reviewed

The use of the shape of extrasystoles as an additional criterion for the localization of the site of myocardial infarction is briefly discussed

Auricular Extrasystoles

The nearer to the normal pacemaker an auricular extrasystole originates the more closely does its P wave resemble that of the sino auricular beats Lewis who established this fact in 1910 distinguished three main types according to the shape of the P waves in lead 2 namely origin of the ectopic beat in the upper auricular portions characterized by upright P waves in the lowest regions of auricular musculature showing inverted P waves and those giving rise to isoelectric or diphasic P waves the origin of which he believed to be in the middle portions of the auricle It was subsequently realized that the shape of the P wave of an auricular extrasystole cannot unreservedly be taken to indicate its site of origin since intra auricular disturbances of conduction may profoundly modify the appearance of these waves More recently attempts have been made to determine the site of origin by the time at which the intrinsic deflection occurs in the oesophageal electrocardiogram immediate occurrence was taken to indicate that the ectopic beat arose in close proximity to the exploring electrode The results so far obtained with recording of intracavity poten tials by means of cardiac catheterization which are briefly discussed have not yet brought any significant advance in our knowledge of this problem To a certain extent this is due to the difficulty in determining the beginning of the intrinsic deflections It is pointed out that in view of the close relationship between auricular extrasystoles and other dis orders of auricular rhythm the study of the site of origin of auricular ectopic beats may well be of a *greater importance than is attached to it at present* since it is likely to result in a better understanding of auricular arrhythmias generally

Origin of Extrasystoles and Specialized System

Regarding the question whether extrasystoles originate only in the specialized system or whether they can arise in the common myocardium the relevant literature is reviewed It is concluded that in certain experimental conditions ectopic impulse formation is possible in any part of the heart In view of more recent findings that the ramifications of the special ized system are far more extensive than previously assumed it remains undecided whether the presence of specialized fibres is indispensable for the origin of ectopic beats

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CHAPTER XI

SOME MAINLY CLINICAL ASPECTS OF EXTRASYSTOLES AND OF ECTOPIC BEATS GENERALLY

EXERCISE

The usual effect upon extrasystoles of physical exercise is their disappearance during and immediately after exertion In a minority of cases exercise precipitates or increases the number of previously present extrasystoles Increase in rate of ectopic tachycardia resulting from physical exertion is observed in rare instances Each of these possibilities merits a brief discussion

Disappearance of Extrasystoles on Exertion

Magnan s observation (1877) that exercise abolished certaines intermittences du pouls may well have referred to extrasystoles In clinical practice it is indeed a common experience that a patient seeks medical advice because he is worried about his heart missing beats which he noticed after going to bed or on other occasions when he was at rest whereas he forgets all about it while going about his daily routine what sensations the premature beats may have caused in the individual case disappear with the extrasystoles during activity Such observations indicating that the arrhythmia occurred only during rest and was abolished by even mild exertion are of diagnostic as well as therapeutic interest diagnostic because if extrasystoles are absent during examination such a history points strongly to their being the cause of the symptoms (*see* section on Differential Diagnosis) therapeutic because lay people often realize nowadays that structural heart disease tends to manifest itself during exertion rather than during rest and thus the patient s own observation about the timing of his trouble suitably explained can with advantage be used to convince him of the harmlessness of his complaint

The disappearance of extrasystoles as a result of exercise is partly due to the ensuing increase in heart rate with shortening of the diastolic intervals and partly to nervous influences upon the heart (*see* chapter on Nervous System)

An unusual observation in which exercise converted ventricular tachycardia with alternation of the complexes in the electrocardiogram into sinus rhythm—a particularly striking example of suppression of an ectopic arrhythmia by exercise—is a case described in a somewhat different context by Scherf and Kisch (Case 2) The patient a man of twenty one (who had always been healthy except for measles and scarlet fever in childhood) fainted during a game of football and subsequently suffered from palpitation Electrocardiograms showed series of extrasystoles and paroxysms of ventricular tachycardia with alternation of complexes (Fig 187a) They were separated by one or two sinus beats (Extrasystolie a paroxysme tachycardiques) Moderate exercise (40 genuflexions) converted the tachycardia into bigeminal rhythm with constant shape of the extrasystoles (Fig 187b) Fig 187c taken five minutes after the end of exercise shows that the ventricular tachycardia re-established itself In this patient more severe exertion resulted in the temporary establishment of sinus rhythm as illustrated by Fig 188 obtained on another day Fig 188a demonstrates bigeminal heart action after moderate exertion (30 genuflexions) When at this

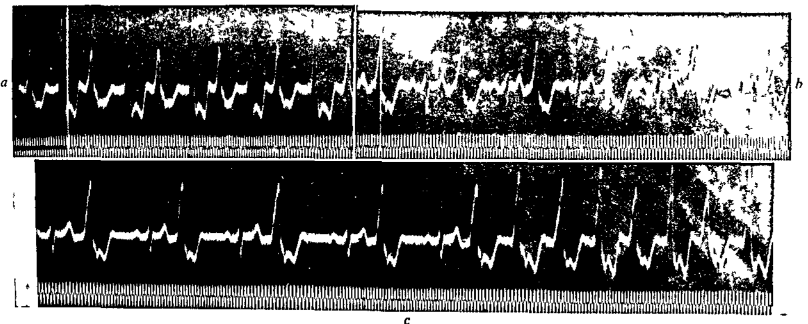


FIG 187—*a* Before exercise Ventricular tachycardia with alternation of shape of the ventricular complexes *b* after moderate exercise Bigeminal rhythm *c* five minutes after the end of exercise Re-appearance of ventricular tachycardia

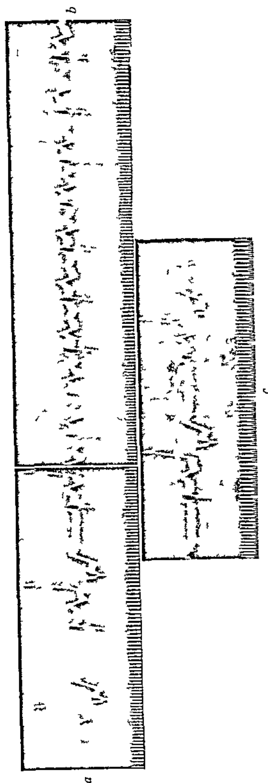


Fig 188.—*a* After moderate exercise Bigeminal rhythm *b* After the same amount of exercise carried out again after the recording of *a* Sinus rhythm *c* Five minutes after *b* Recurrence of bigeminal rhythm

stage the same amount of exercise was carried out again sinus rhythm ensued (Fig 188b) but five minutes later bigeminal heart action was again present (Fig 188c)

In this case in which also digitalis and quinidine abolished the arrhythmia temporarily it was not possible to restore sinus rhythm for any length of time and the patient died after five years from congestive heart failure Necropsy showed a grossly enlarged heart without hypertrophy or any structural (macroscopic or microscopic) abnormality—a remarkable illustration of fatal myocardial weakness resulting entirely from disturbances in the cardiac dynamics

Precipitation of Ectopic Arrhythmias by Exercise

The reverse effect upon extrasystoles of exercise namely precipitation of the arrhythmia or increase in the number of previously present premature beats while not so common is by no means rare Patients responding to exertion in this way usually but not invariably suffer from structural or toxic heart disease A few relevant papers may be briefly discussed

In an investigation on thirty five normal children with extrasystoles Lyon and Rauh found after exercise an increase in the number of the premature beats in four and a decrease in fourteen cases

Bourne examined this question in normal subjects and in patients with various forms of heart disease During the period after exercise in which the heart rate dropped to its resting level seven out of eight normal subjects showed a decrease in the number of extrasystoles or no change was observed In patients with rheumatic heart disease similar conditions were found In nine out of eleven patients with arteriosclerosis on the other hand the number of premature beats increased after exercise We concur with Bourne s interpretation that this was due to ischaemia in some parts of the heart resulting from coronary sclerosis Such increase in the number of premature beats after exertion was seen by several investigators (arhythmie d effort crises extrasystoliques Josue and Heitz Luten Wilson and Robinson Otto and Gold Gallemaerts and van Dooren)

Klemola studied this problem especially in connexion with infectious diseases Amongst 215 patients who had just recovered from some infectious illness extrasystoles after exercise were found in twenty seven eighteen of these had had diphtheria the remaining nine some other infection (for instance tonsillitis scarlet fever pneumonia) In twenty three of these cases extrasystoles occurred only after exertion (Klemola 1942) In a later study devoted to the effects of diphtheria in children he found extrasystoles after exercise in eighteen out of forty one cases in seventeen of these the premature beats occurring only after exertion (Klemola 1944)

Kienle considers as pathological all extrasystoles which occur immediately or within a few minutes after exercise According to him an abnormal condition of the heart must be assumed also if exercise fails to abolish existing extrasystoles

A personal observation may be added in which exercise precipitated not only extrasystoles but also paroxysmal tachycardia (Scherf 1924) (*see also* Gallavardin) The records (Fig 189) were obtained from a forty four year old woman without evidence of heart disease who complained of palpitation on exertion At rest this patient always showed sinus rhythm (Fig 189a) Twenty five genuflexions precipitated ventricular paroxysmal tachycardia the rate of which was 212 per minute but soon dropped to 183 (*see* Fig 189b and c) As the rate slowed down further an increasing number of sinus beats were observed separated by a steadily diminishing number of extrasystoles (*see* Fig 189, d and e) until finally sinus rhythm was re-established In this patient exercise had invariably the described effect upon the cardiac rhythm

Denolin reported a case of complete A V block in which exercise precipitated attacks

of paroxysmal ventricular tachycardia with varying shape of the ectopic ventricular beats

There is ample evidence of auricular fibrillation occurring after exercise in healthy subjects (Jervell Kienle)

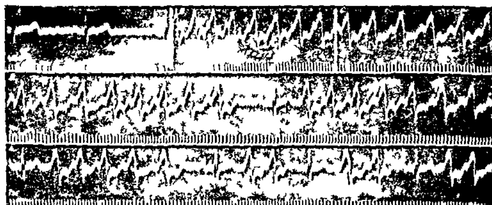


FIG 189—*a* At rest Sinus rhythm *b–e* various degrees of ectopic ventricular tachycardia and arrhythmia after exercise Time base 0 04 second From SCHERF *Wien Arch inn Med*

Increase by Exercise of the Rate of Ectopic Tachycardia

This effect of exercise upon ectopic—auricular or ventricular—tachycardia is rare Instances have been described by Wenckebach and Winterberg Wilson *et al* (1932) Scherf and Weissberg Fig 190 taken from Scherf and Weissberg s paper (Case 4) provides an example It was obtained in a man of forty eight a heavy smoker who complained of precordial pain and palpitation on exertion At rest ventricular extrasystoles occurring in



FIG 190—Lead 2 Increase in rate of ventricular ectopic rhythm from 100 (a) to 130 (b) resulting from moderate exercise Time base 0 04 second

groups of four or five were present some slowing of the ectopic rhythm being observed in respect of the last two extrasystoles of each group After exercise (knee bending fifteen times) the number of extrasystoles increased considerably as well as their rate for example from 100 to 130 (*see* Fig 190b as compared with Fig 190a) It is reasonable to assume that

this was due to a sympathetic nervous effect this view is supported by the experimental observation that stimulation of the sympathetic increases the rate of ectopic ventricular tachycardia produced in dogs by the focal application of hypertonic solutions of barium or sodium chloride to the epicardial surface of the exposed heart *in situ* (Piccione and Scherf)

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POSTURE

The frequent occurrence of extrasystoles in the supine position is a well known fact A great many patients find that they are only or mainly aware of the missed beats when they are in bed and settling down for a night s rest Several factors are likely to be responsible during the daily activities the patient s attention is diverted whereas at night such arrhythmias are more likely to obtrude themselves the slower heart rate and nervous factors also play their part Many patients however insist that rest in a chair will not precipitate the arrhythmia whereas the horizontal position will invariably do so Moreover in some individuals extrasystoles occur only while lying on one particular side There is thus a definite positional element in a proportion of cases

Lyon and Rauh found in twenty two children that change from the supine to the erect posture increased the number of extrasystoles in four and decreased it in seven instances

An observation of ventricular extrasystoles (namely short runs of ventricular tachycardia) occurring in an otherwise healthy woman of twenty four only on assuming the erect posture was reported by Peters and Penner it was attributed to an unusually strong sympathetic tone on this change of position An increase in the number of extrasystoles and the occurrence of auricular paroxysmal tachycardia on assuming the erect posture were observed by Fine and Miller in a girl of sixteen

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EXTRASYSTOLES IN RELATION TO VARIOUS TYPES OF CARDIOVASCULAR DISEASE

Coronary Disease

Experimental Investigations

Arrhythmias following ligation of coronary artery branches were observed long before any detailed analysis of such irregularities by modern methods was possible (Bezold 1867 Porter 1894 1896) and the importance of such disturbances of rhythm in causing sudden death of patients with coronary disease was recognized by Cohnheim and Schulthess Rechberg as early as 1881

In the first systematic investigation on cardiac arrhythmias elicited in dogs by ligation of the descending branches of the right or left coronary artery extrasystoles were recorded (Lewis 1909) Usually such ectopic beats were ventricular in origin but after ligation of the right coronary artery nodal and auricular extrasystoles were also observed (Lewis Smith Kisch) The shape of the extrasystoles varied continually and sometimes ventricular extra systoles with retrograde conduction to the auricles as well as interpolated varieties were seen In some experiments however extrasystoles were completely absent

The time of occurrence of such ectopic beats varies often they are observed within one minute after ligation but sometimes a much longer interval elapses for example forty six minutes (Goldenberg and Rothberger) or even one week as observed in one monkey by de Waart Storm and Koumans (1936b)

The incidence of ectopic beats after ligation of coronary branches varies according to different investigators but seems to be about 35–50 per cent on an average Thus Harris and Hussey saw them in fifteen out of fifty dogs within fifteen minutes after ligation followed by ventricular fibrillation In monkeys de Waart and collaborators saw them in six out of seventeen experiments following ligation of the descending branch of the left and in six out of fifteen instances after that of the right coronary artery In another series (Blumgart Gilligan and Schlesinger) in which nembutal and ether were used as anaesthetics they occurred in 50 per cent of thirty nine dogs and were observed particularly frequently in those which later developed ventricular fibrillation The one dissenting report of Damir and Lampert that up to three hours after ligation of coronary arteries no extrasystoles were observed in dogs anaesthetized with morphine and ether can be disregarded This report is strange because in six out of ten dogs coronary artery ligation (*ramus descendens ant*) caused ventricular fibrillation and paroxysmal tachycardias were also observed

No constant relationship seems to exist between the site of origin of ventricular extra systoles and that of the ligated coronary artery branch In one series of experiments only were right ventricular extrasystoles found after ligation of the right and left ventricular ones after that of the left coronary artery (Clerc Deschamps Bascourret and Levy) but all other investigators reported right or left ventricular ectopic beats with ligation of either coronary artery This is rather surprising in view of the available evidence discussed on p 401 and below in this section (p 420) that the ectopic beats originate in the boundary zone between the ischaemic and non ischaemic areas

In a typical experiment extrasystoles occur at first singly Then the intervals between the ectopic beats become successively shorter while their number increases The next stage is polygeminy and short attacks of ectopic tachycardia follow culminating in flutter and

fibrillation In some experiments ventricular fibrillation sets in without extrasystoles having previously occurred this was observed in six monkeys by de Waart and his collaborators In other experiments extrasystoles gradually disappear without any more pronounced arrhythmia occurring Longer chains of bigeminal rhythm are decidedly rare

As had to be expected injection of obliterating substances into the coronary artery has the same effect as ligation (Hamburger Priest and Bettman) When in cats air was injected into the jugular vein extrasystoles originating in the right ventricle were recorded with injection of air into the left ventricle the extrasystoles originated in that ventricle (Pines) Fat embolism has been seen to produce extrasystolesin man (unpublished personal observation)

In spite of extensive experimental investigations the underlying mechanism is only partially understood Spasm originating by way of reflex from the infarcted area through the vagus as efferent nerve has been claimed as being partly responsible for such arrhythmias (Manning *et al* LeRoy and Snyder) It was found that as compared with conscious dogs the mortality after coronary ligation in animals anaesthetized with morphine and ether was reduced from 40 to 10 per cent This difference was thought to have been probably due to vagal paralysis (Manning *et al*) We are not in agreement with this view for several reasons Amongst them the failure of an antispasmodic drug such as aminophylline to prevent such arrhythmias may be quoted (Mahaim and Rothberger) The absence of struggling of the anaesthetized animals may also well have been of importance in accounting for the above differences

Quinine also was incapable of preventing such arrhythmias In seven experiments 0 2–0 4 gramme of quinine was injected into dogs immediately after the first ectopic beats had occurred but in five experiments ventricular tachycardia and in four ventricular fibrillation were recorded (Goldenberg and Rothberger) Further data on the effect of quinidine in such arrhythmias are given in the section on this drug (p 292)

General asphyxia of the heart also cannot be considered to play any significant part for ectopic arrhythmias do not occur in such circumstances (Mathison Lewis and Master Motta) though disturbances of conduction and shifting of the pacemaker were seen (Greene and Gilbert) In extrasystoles elicited by aconitine even the reverse effect of asphyxia was observed by Scherf who found it to abolish the extrasystoles in fifteen out of nineteen experiments

In contradistinction to the failure of *general* asphyxia of the heart to have any effect upon ectopic rhythm formation that of *local* ischaemia has increasingly been realized as of great importance Harris and Rojas put forward good reasons for the assumption that after ligation of coronary branches the ectopic beats originate in the ischaemic nonischaemic boundary zone Local leads obtained from this zone showed abnormally high spikes and also monophasic R T segments These authors also drew attention to the striking similarity between such rhythms developing as a result of regional ischaemia and those elicited by galvanic current and concluded that certain alterations in the permeability conditions of the cells of that zone may be the common factor Harris and Matlock found in the mammalian heart that moderate anoxia lowered the threshold to brief electrical stimuli whereas in severe anoxia the threshold rose rapidly In excised nerve Lehmann found a transient increase in excitability occurring during the first six to eight minutes of asphyxia during this period spontaneous discharge of impulses may occur This whole aspect is discussed in more detail in the chapter on Mechanism

Wiggers Wegria and Pinera showed in experiments on dogs that one to two minutes after occlusion of the *ramus descendens* the fibrillation threshold to rectilinear D C shocks of 0 01–0 02 second applied in the vulnerable period after a contraction was considerably reduced At the same time centres of ectopic impulse formation occurred in such circumstances On the basis of such observations these authors put forward certain views on the

mode of origin of ventricular fibrillation occurring after coronary occlusion In essence these consist in the assumption that ventricular fibrillation is precipitated by ectopic beats becoming supra threshold as a result of the lowering of threshold and that any one of them may thus initiate ventricular fibrillation when it falls in the vulnerable period of either a normal beat or of an ectopic one originating from another ectopic focus This aspect is discussed more fully in the section on Fibrillation

Because of the delayed appearance of extrasystoles after myocardial infarction it was claimed that they originate in the area of inflammation surrounding the infarcted area (Froment) Rothberger and Zwillinger found that after ligation of a coronary artery branch smaller doses of strophanthin produced ectopic arrhythmias since the drug could not have reached the infarcted area these authors tentatively concluded that the ectopic beats arose in the zone surrounding the infarct These views seem compatible with the assumption of Harris and Rojas

More recently Harris (1950) studied such ectopic rhythms in greater detail By effecting the ligation (of the anterior descending artery in dogs) in two stages within an interval of one hour he succeeded in avoiding the onset of ventricular fibrillation and was thus able to investigate delayed ventricular ectopic rhythms In such experiments ectopic beats were observed within the first ten minutes after the completed occlusion A quiescent period followed of four and a half to eight hours during which little or no ectopic activity was recorded After this latency ectopic beats developed with increasing frequency the duration of the ectopic activity varying between two and five days While the immediate ectopic rhythm was attributable to the effect of local ischaemia via injury potentials the long period of delayed ectopic activity was considered mainly due to the effect of products of necrosis

Clinical Observations

These are on the whole in accordance with the experimental findings Ventricular extrasystoles and paroxysmal tachycardia following coronary occlusion were reported by Robinson and Herrmann in 1921 and Ebstein and Mackenzie saw extrasystoles frequently during attacks of angina pectoris

A few data about the incidence of such arrhythmias in myocardial infarction may be useful Rosenbaum and Levine saw extrasystoles in 25 per cent of their cases with coronary thrombosis amongst them ventricular as well as auricular ones As the mortality was 27 per cent in the patients without and 33 per cent with extrasystoles these authors denied any prognostic significance of extrasystoles in this condition This conclusion is not in accordance with our experience and that of others and may be due to the fact that these authors used quinidine in adequate doses once such arrhythmias were noticed

Similar findings were obtained by Master Dack and Jaffe

Padilla and Cossio reported extrasystoles in twenty out of ninety two cases of myo cardial infarction Of these twenty eight (40 per cent) died including all four patients with multiform extrasystoles The mortality of the patients without extrasystoles was 38 per cent Woods and Barnes encountered an incidence of extrasystoles of 11 2 per cent in those of their patients who survived and of 23 3 per cent in those who succumbed The number of extrasystoles also seems of importance occasional extrasystoles not more than one in twenty one beats were seen in three patients who survived and in another three survivors ectopic beats occurred once in eleven to twenty beats More numerous extra systoles were recorded in seventeen cases 82 4 per cent of whom died

In Jervell s series of sixty five patients with myocardial infarction supraventricular extra systoles were found in nine ventricular ones in twenty three and both types in two in stances

Smith Keyes and Denham studied the records of 920 patients with acute myocardial

infarction followed up for six weeks Arrhythmias in some form were found in 16 3 per cent of these extrasystoles were commoner than any other form the incidence being 7 7 per cent Sixty three patients had ventricular extrasystoles with twenty three deaths (mortality of 35 6 per cent) Of these twenty six had not received quinidine and ten died (38 4 per cent) and of the remaining thirty seven who were given quinidine thirteen died (35 1 per cent) Seven had auricular extrasystoles of whom one died and one had nodal premature beats Total Seventy one patients of whom twenty four died (33 8 per cent) These authors think that extrasystoles occur more frequently than these figures would indicate also that the presence of extrasystoles had a bearing on the mortality rate This was particularly high in the thirteen patients with ventricular tachycardia of whom eight died (61 5 per cent)

Two rather unusual personal experiences may briefly be mentioned they are illustrated in Fig 191 Both records were obtained in patients with a recent infarction in the posterior wall The top tracing shows—in addition to the usual features of the ventricular complexes—auricular extrasystoles with aberration of the ventricular portion of the first extrasystole of each series and short paroxysms of auricular fibrillation The bottom tracing reproduces an unusual monophasic record with numerous ventricular extrasystoles Both patients survived the attack

In some patients with myocardial infarction the shape of extrasystoles may suggest the diagnosis in the absence of diagnostic features of the sinus beats Some instances are described in the sections on Ventricular and Auricular Extrasystoles (pp 31 and 52)

Auricular extrasystoles are more common in infarction of the posterior wall this is understandable since the sinus node and large portions of the auricles are supplied by the right coronary artery

Abnormalities of the auricular mechanism including auricular extrasystoles are also found more frequently in auricular infarction that of the right auricle being more common than of the left This has been found experimentally as well as clinically (Cushing Feil Stanton and Wartman Schott)

Since the occurrence of extrasystoles in acute myocardial infarction often is a danger signal and more numerous ventricular ones may be the precursors of ventricular tachycardia with the ominous risk of sudden death from ventricular fibrillation the routine exhibition of quinidine (*see* p 475) as a preventive has been suggested in all patients with acute myocardial infarction (Morawitz and Hochrein) In a large hospital quinidine in doses of 0 1 gramme twice daily was routinely given to all patients with aortitis and coronary sclerosis and its exhibition continued throughout the patients stay in the hospital sometimes for months This method was claimed successful on the grounds of the following data in the year before the medication was introduced (1927) twenty four patients died suddenly the presumed cause of death being ventricular fibrillation In the following year 1928 the first during which this method was applied only five instances of sudden death were observed The total number of patients was about seven thousand a year The validity of this conclusion seems to us doubtful in view of the long intervals between the exhibition of such small doses of the drug which is eliminated so quickly There is also no experimental evidence that quinidine prevents ventricular fibrillation after coronary ligation However similar good results were reported by Borg In his series the mortality due to sudden death dropped from twenty three in 1935 to five in 1936 when the routine exhibition of quinidine (0 2 gramme three times a day) was instituted

Since in a large proportion of patients with extrasystoles after coronary occlusion the ectopic beats disappear after quinidine medication it is recommended to give quinidine sulph 0 15–0 2 gramme every four hours for the first three weeks following the infarction in all cases This is not done universally but quinidine should certainly be given in every case of coronary occlusion in which extrasystoles occurred (except isolated ones at

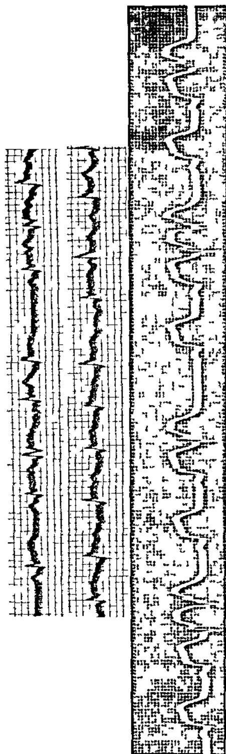


Fig 191 —Both records lead 3 Both from patients with a recent infarction in the posterior wall *Top record* The two tracings are continuous Auricular extrasystoles with aberration of the ventricular portion of the first extrasystole of each series also short paroxysms of *auricular fibrillation* *Bottom record* Unusual *monophasic* complexes with numerous ventricular extrasystoles

very long intervals) If necessary for the suppression of the arrhythmia the dose may be increased

Ventricular extrasystoles are often encountered in patients with coronary sclerosis without myocardial infarction or angina pectoris Not infrequently they are the first manifestation of the disease particularly in men over forty They occurred in forty two instances amongst 974 cases of coronary sclerosis that is in 5 5 per cent (Cowan and Ritchie)

In such cases extrasystoles may occur after exertion or immediately after an exercise test (Goldhammer and Scherf) and usually show varying shapes in the electrocardiogram Since in subjects without myocardial disease extrasystoles as a rule disappear during and immediately after exertion the above observation is of diagnostic importance In some instances the occurrence of extrasystoles during exertion coincides with the onset of angina of effort and the arrhythmia subsides with the pain (Mathieu Wayne and Laplace Proger Minnich and Magendantz Porter 1948)

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Hypertension

The question of the incidence of extrasystoles in hypertension is of interest from various points of view

For a long time on experimental grounds a disproportion between the contractile power of the heart and the arterial resistance was considered an important cause of arrhythmias (*see* chapters on Historical Remarks and on Extrasystoles and the Nervous System) In this connexion de Heer s finding of extrasystoles in pronounced experimental aortic stenosis is not infrequently quoted

Clinically this problem is of interest in view of the very common occurrence of hypertension

Figures in the literature vary greatly Warkentin reported no effect of raised blood pressure on the incidence of extrasystoles whereas Peel found an incidence of 26 per cent amongst 184 patients with hypertension The figures of other investigators fall between such extremes for instance an incidence of 7 per cent found by Koppang and of 3 5 per cent in eight hundred uncomplicated cases of hypertension by Flaxman In the latter series the immediate mortality of patients with extrasystoles was only slightly higher than the average of the whole series

Wenckebach and Winterberg stressed the difficulties in arriving at accurate figures Amongst the total of their cases with extrasystoles 8 per cent had hypertension A more reliable method seemed to these authors to determine the incidence of extrasystoles in 408 patients with hypertension Of these 243 had a systolic pressure exceeding 190 mm Hg and twenty six (11 25 per cent) had extrasystoles amongst the remaining 165 patients with a blood pressure of 150–190 the incidence of extrasystoles was eighteen (11 1 per cent) *From these figures Wenckebach and Winterberg concluded that neither the height of the* blood pressure nor the presence of hypertension *per se* had any significant effect on the incidence of extrasystoles This view was supported by the small number—twenty six—of patients under forty in a series of 385 hypertensives since in that younger age group the incidence of extrasystoles is known to be high

According to Fishberg arrhythmias are common in the failing hypertensive heart and extrasystoles are perhaps the most frequent form of irregularity However this holds good also for normal subjects

Such discrepancies in the findings of the various investigators are not surprising since this problem is complex On the one hand it is common clinical experience that multitudes of hypertensives have no arrhythmia On the other in those exhibiting extrasystoles other factors are likely to be of importance Of these coronary sclerosis takes first place its presence in a large proportion of middle aged and elderly hypertensives is most probable Moreover the influence of nervous and hormonal factors discussed in the appropriate sections is of equal importance Regarding the former the proneness of many hypertensives to emotional instability needs no stressing Concerning the latter the appearance of extrasystoles during a hypertensive crisis in patients with a phaeochromocytoma of the suprarenals (Hegglin and Holzmann) provides an instructive example Here it seems reasonable to assume that not the hypertension *per se* but the circulating pressor amines (epinephrine and *nor* epinephrine) are responsible for the arrhythmia

The observation made more recently by Scherf Scharf and Goklen that in certain experimental conditions stretching of the auricles may precipitate auricular ectopic beats points to the importance of mechanical stretching in this connexion but this finding cannot without reserve be applied to the human heart However the occurrence of paroxysmal tachycardia and particularly of auricular fibrillation after unusually heavy exercise has often been reported in subjects with normal hearts and it is thus quite possible that acute dilatation of the heart may precipitate extrasystoles in some cases

SUMMARY

Chronic uncomplicated hypertension cannot be considered to favour the occurrence of extrasystoles Pronounced acute rise in blood pressure seems in some healthy subjects to cause ectopic beats the stretching of the cardiac chambers possibly being a precipitating factor

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Trauma

Since any slight mechanical stimulation of the heart may cause extrasystoles it is not surprising that they are found in cases of penetrating injury of the heart (stab or gun shot wounds) and it is very probable that premature beats occur in most cases at the moment of accident

During surgical manipulation of the heart extrasystoles occur frequently it has been proposed to prevent such arrhythmias by means of procaine (*q v*) *In* cases of injury to or ligation of a coronary artery extrasystoles are likely to occur for longer periods and *constitute a dangerous complication*

Non penetrating injury causing concussion and contusion of the heart may also cause extrasystoles Blunt trauma to the chest wall particularly to the praecordial region may produce an area of myocardial necrosis which just as in cases of myocardial infarction after a short time sets up an inflammatory reaction Moreover haemorrhages occur in all layers of the heart In these circumstances extrasystoles were seen clinically as well as experimentally

Clinical Observations Since a considerable number of clinical instances had been reported before this problem was first investigated experimentally in detail the clinical aspect is discussed first

Amongst ninety cases of non penetrating injury to the heart Warburg (1938) encountered extrasystoles in nine instances and in a subsequent series of fifty nine cases in two (Warburg 1940) Similar findings were published by others (Kahn Barber) Such statistical data are however to be u ed with re erve for the presence of extrasystoles occurring independently of trauma has to be considered moreover in those instances in which extrasystoles developed as the result of trauma they may well be absent during the short period of examination or may have already disappeared by that time In one case reported by Hyman and Fisher left ventricular extrasystoles were observed post operatively after a stab wound in the base of the left ventricle In Baledent and Bizard s case the extrasystoles had an unexpected shape in the electrocardiogram considering the site of the traumatic lesion

Experimental Investigations Moritz and Atkins produced blunt cardiac trauma in thirty two dogs extrasystoles were observed in five The anatomical examination showed local contusion in two animals and failed to reveal any injury in the remaining three Others (Kulbs Schlomka and Hinrichs Beck Bright and Beck) also observed extrasystoles following blows applied directly to the expo ed heart and those to the intact chest wall

Similar findings were obtained by Scherf and Terranova from whose experiments Figs 192 and 193 are taken

Fig 192 was obtained from a cat By means of a guillotine like device a weight of 2 kg was made to fall on the praecordial area from a height of 100 cm A ventricular tachycardia appeared *immediately after the trauma This was followed by ventricular extrasystoles* which had the same shape as the abnormal beats during the preceding tachycardia and which often occurred as coupled beats In other experiments auricular extrasystoles occurred immediately after the trauma (Fig 193) Such arrhythmias as well as auricular fibrillation which was commonly observed in such experiments disappeared within a few minutes The experiments were not carried out sufficiently long for studying the possible re appearance of the ectopic beats this might well be expected in view of the reactive changes in the injured tissue discussed above

Regarding the mechanism underlying such arrhythmias Schlomka and Hinrichs ascribed them to vasospasm consequent upon the trauma In our opinion it is far more *likely that they were due to the mechanical stimulus and damage of the* trauma The arrhythmia—as well as changes in the final deflections—occurred instantaneously after the trauma and the interval is thus too short as for vasospasm to account for the disturbance

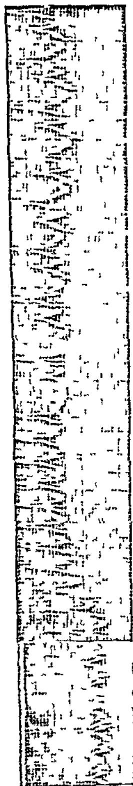


Fig 192.—From an experiment on a cat *a* Before trauma Sinus rhythm *b* After blunt trauma to the chest wall Ventricular tachycardia and bigeminal rhythm

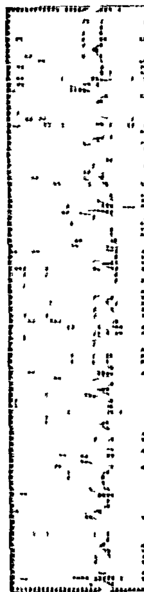


Fig 193.—From an experiment on a cat Auricular bigeminy after blunt trauma to the chest wall

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Catheterization

With the increasing use made of catheterization of the heart disorders of cardiac action elicited by this procedure are assuming great clinical importance Amongst these ectopic arrhythmias are frequent and their study is also of considerable physiological interest It has of course been known for a very long time that experimentally even slight mechanical stimulation of the epicardial and particularly of the endocardial surface elicits abnormal contractions

Extrasystoles were reported soon after catheterization was employed more widely Bloomfield *et al* found ventricular ectopic beats frequently in seventy seven catheterizations on seventy subjects and considered the arrhythmia probably due to contact of the tip of the catheter with the heart Sosman encountered extrasystoles in about one half of a hundred cases when the catheter was passing through the tricuspid orifice Dexter *et al* reported cardiac irregularities during catheterization in twenty seven out of forty two patients demonstrated by electrocardiogram pulse tracings or palpation and ventricular extra systoles in five out of twelve patients with repeated electrocardiograms In a later study (Levine *et al* see below) it was found that the incidence of ventricular extrasystoles actually is considerably higher than this early study seemed to indicate

In an early paper on intracavity electrocardiograms Hecht (1946) obtained in one case records of auricular and ventricular extrasystoles while recording the right auricular electro endocardiogram by means of an intracardiac lead Battro and Bidoggia also using intra cavity leads emphasized the similarity in shape of right ventricular extrasystoles in the right auricular electroendocardiogram and the right precordial leads also lead aVR left ventri cular extrasystoles which occurred during catheterization showed an initial upstroke in leads obtained from the right auricle and right ventricle The bearing which the findings of these authors have on the localization of the focus of origin of ectopic beats is discussed in the appropriate chapter (p 399) In the right auricular cavity record of auricular extra systoles their P waves started without the initial upstroke of the P waves of sinus beats which was interpreted as indicating a focus of origin of such extrasystoles beneath the exploring electrode in the right auricle

Levine *et al* employing intracavity leads emphasized the relative rarity of auricular extrasystoles with the catheter in the right auricle as compared with that of ventricular ones with the catheter in the right ventricle Auricular extrasystoles were found in only four out of twenty one cases and occurred mostly as single ectopic beats Their shape indicated that they were precipitated by the catheter With the catheter in the right ventricle on the other

hand ventricular premature beats or paroxysms of ventricular tachycardia occurred in the vast majority of the series of twenty seven cases Such arrhythmias invariably dis appeared when the tip of the catheter was advanced into the pulmonary artery or withdrawn into the right auricle These authors assume that the ectopic beats were due to contact of the tip of the catheter with the right ventricular endocardium of the interventricular septum The reason for the more frequent occurrence of ventricular as compared with auricular ectopic beats is believed by these authors to be that in the auricle the intracardiac electrode is more prone to remain in midstream and therefore not placed in a position favourable for precipitating extrasystoles by being in intermittent contact with the wall of the chamber as is the case in the ventricle We should like to add as another probable reason that specialized tissue is present throughout the ventricles whereas in the auricles it is limited to the S A and A V nodes Some further details about the electrocardiographic appearance of such ectopic beats are discussed on p 399

Some impression of the incidence of such arrhythmias in connexion with cardiac catheterization may be conveyed by Table 4 (p 433)

In the series of 133 catheterized patients of Michel *et al* the incidence of arrhythmias was found twice as high in patients with congenital heart disease as in the remaining group of acquired (mostly hypertensive and coronary) cardiac lesions it was also significantly higher in patients with pre existing electrocardiographic abnormalities

A few individual points may be briefly mentioned

The predominence of ventricular over auricular ectopic beats is mentioned by most investigators for example Levine *et al* Goldman *et al* Landtman Ravin *et al* Michel *et al* Most authors also express the opinion that the ectopic beats are elicited mechanically by the contact of the tip of the catheter with the endocardial wall However the various portions of the heart vary in their propensity to develop ectopic rhythms

In the electrocardiographic study in connexion with angiocardiography of Biorck *et al* premature beats occurred in all twenty one cases injected by a catheter into the right auricle right ventricle or pulmonary artery whereas none were observed in the cases in which the injection was given into the superior vena cava (three) or in the aorta (twenty two) Landtman found that such arrhythmias were elicited most readily from the infundibulum of the right ventricle the area near the tricuspid valve and the remaining part of the right ventricle whereas they occurred far less frequently from the stem or branches of the pul monary artery or the right auricle The focus of origin was assumed to be the subendo cardial specialized system particularly the peripheral ramifications (Landtman)

The relationship between the mechanical stimulus provided by the catheter and the ensuing arrhythmias seems however to be more complex Ravin *et al* pointed out that ectopic beats elicited from the septum may vary in shape and timing and expressed the opinion that such arrhythmias originated from multiple irritable foci Similar observations were made by Landtman when the tip of the catheter touched the infundibulum (Regarding the determination of the site of origin of ectopic beats generally as mentioned in some of the discussed papers some doubts may be expressed about the validity in those instances in which this was based on the shape of the ectopic beats in only one standard or praecordial lead)

Biorck *et al* remarked that the localization of the tip of the catheter did not seem to decide the type of the premature beats ventricular extrasystoles were seen when the con trast medium was injected into the auricle and auricular premature beats with injection into ventricle or pulmonary artery While these authors assume most electrocardiographic disturbances to be due to some direct mechanical intra cardiac irritation either by the catheter or the spout of the injected medium the possibility of an indirect influence of cerebral and nervous factors will also have to be taken into account

Similar observations were made by Michel *et al* who found in a considerable propor tion of their 133 catheterized patients that intra auricular locations of the catheter tip

were associated with a variety of extra auricular rhythms It appeared difficult to explain the mechanism of impulse origin in these instances except on a basis of reflex excitation of the endocardial or endothelial surface other than the point of impulse formation This view was supported by observations on serious arrhythmias occurring before the inserted catheter had been advanced into the superior vena cava or past the axilla or in one fatal case even immediately following its introduction into the vein

The importance of nervous factors in the causation of ectopic arrhythmias is discussed in the appropriate chapter (p 253) Furthermore such observations recall the experimental findings of Scherf *et al* that in certain circumstances activity of one ventricular ectopic centre may stimulate impul e formation in other ectopic foci

Another form of a possible stimulation of an ectopic focus was seen by Kossmann *et al* using an intracavitary lead This group of workers observed the temporary occurrence in the electrocardiogram of complexes closely resembling pre excitation which they considered due to a temporary increase in excitability of a ventricular centre by the catheter They were led to favour a functional rather than structural explanation of this phenomenon (W P W syndrome) a conjecture at which Coelho *et al* also arrived as a result of similar experimental and clinical observations We do not agree with this view for reasons discussed in the next section (*q v* p 438)

In thirteen of the eighty-eight children with arrhythmias of Landtman s series the tip of the catheter reached the left heart in most of these cases through an inter atrial septal defect and of the fifteen instances of disturbances of rhythm extrasystoles were the commonest Auricular tachycardia was observed in a young child with an inter atrial septal defect when the catheter passed through it (Johnson *et al*)

An unusual observation was made by Ravin *et al* on a patient with spontaneous attacks of auricular paroxysmal tachycardia when during such an attack the catheter entered the right ventricle a ventricular tachycardia was precipitated which subsequently changed into sinus rhythm a truly unique method of stopping a paroxysmal tachycardia Zimdahl reported in a girl of four with an interventricular septal defect an instance of lower nodal tachycardia elicited by the catheter which persisted after the catheter was withdrawn into the superior vena cava and was terminated after thirty minutes by procaine His paper contains a useful summary of experimental and clinical observations on the various disorders of the cardiovascular system during catheterization

In the majority of instances ectopic arrhythmias cease when the location of the catheter is altered or if necessary withdrawn In some cases the exhibition of drugs proved necessary of which procaine quinidine and atropine have been successfully employed Procaine amide (Pronestyl) which has recently been introduced in the treatment of—especially ventricular—ectopic arrhythmias may prove useful in some instances of this kind though we are not aware of any reports yet published on the use of this drug in connexion with cardiac catheterization except in one case in the series of Lasser *et al* (*see also* section on Cocaine p 309)

Considering how widely catheterization is employed fatal ectopic arrhythmias caused by it have been reported in only a small number of cases Nevertheless they are of great clinical significance since they call for immediate change of position or withdrawal of the catheter supplemented in some cases by the administration of drugs they have to be regarded as potentially ominous precursors of fatal ventricular fibrillation

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Extrasystoles and Pre-excitation Syndrome

The pre excitation or Wolff Parkinson White (WPW) syndrome is characterized in the electrocardiogram by abnormally short P R intervals followed by QRS complexes of abnormal shape and increased width The latter indicate anomalous intraventricular conduction

The syndrome is now generally accepted as being due to the conduction of the S A im *pulse to the ventricles by an abnormal pathway namely an accessory A V connexion*

The condition is often found in otherwise normal subjects Numerous instances were published as a result of electrocardiograms taken during the war in service personnel with out any evidence of structural heart disease Grave and even fatal cases showing this syndrome have however been reported (Broustet *et al*)

The frequent occurrence in this condition of attacks of paroxysmal tachycardia is univer sally recognized Scherf and Schönbrunner found a history of such attacks in twenty out of thirty five cases with this type of electrocardiogram In his comprehensive paper on the pre excitation syndrome Oehnell reported paroxysmal tachycardia in 70 per cent of a large number of cases collected from the world literature Schott described this association in an infant of eight months

Auricular and ventricular extrasystoles also occur in the WPW syndrome but as dis tinct from the association with paroxysmal tachycardia only comparatively few cases have been published (Scherf and Schonbrunner Littmann and Tarnower)

Fig 194 was obtained from a forty six year old man who stated to have always been healthy except for occasional attacks of palpitation Examination revealed a WPW syn drome which disappeared after exercise (*see* Scherf and Schonbrunner) Fig 194a shows

TABLE 4

Ectopic arrhythmias observed in connexion with cardiac catheterization

No of Cases	Extrasystoles						Tachycardia						Remarks	Author
	Auricular		Nodal		Ventricular		Auricular		Nodal		Ventricular			
	No	Per cent	No	Per cent	No	Per cent	No	Per cent	No	Per cent	No	Per cent		
23	17	74	8	35	0	87	2	8 7	—	—	—	—	Twenty two patients had tuberculosis one asthma	Ravin *et al*
50	30	60	39	78	44	88	7	14	9	18	39	78	Thirty six had congenital heart disease All patients showing auricular or nodal tachycardia had congenital heart disease Ventricular tachycardia diagnosed when more than 3 ventricular extrasystoles occurred in succession Auricular flutter in 3 patients auricular fibrillation in none	Goldman *et al*
142	31	72 (36)	7	5 (8)	69	49 (79)	2	1 4 (2 2)	—	—	2	15 (5)	All children One hundred and sixty cardiac disturbances observed in 88 of the 142 The percentage incidence of the listed arrhythmias amongst these 88 is given in parenthesis	Landtman
133	3	4	—	—	35	55	2	3	—	—	14	24	The figures refer to numbers and percentage of incidence from Table 2 of original	Michel *et al*
49	7	14	11	22	33	66	6	12	—	—	12	24	Forty three records from patients with congenital heart disease 4 normals 2 with rheumatic valvulitis Ventricular tachycardia defined as runs of 3 or more ventricular extrasystoles	Lasser *et al*

the typical features of the WPW syndrome with an auricular extrasystole following every or every second sinus beat The P waves of the extrasystoles are visible in the T waves of the preceding beat Fig 194b also shows auricular extrasystoles one occurred after the

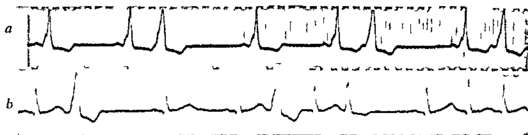


FIG 194 —*a* and *b* from the same patient Pre excitation syndrome with auricular extrasystoles For explanation see text From SCHERF and SCHONBRUNNER *Z klin Med*

first normal sinus beat the third sinus beat is followed by three auricular extrasystoles and another two are seen at the end of the tracing These extrasystoles show three kinds of QRS complexes some resemble those of the normally conducted sinus beats others are very similar to those of the sinus beats with anomalous intraventricular conduction and others again for instance the last of the three extrasystoles following the third sinus beat have an intermediate shape The assumption seems justified that some of these premature beats were normally conducted through the A V bundle some of them through an accessory bundle and some simultaneously over both pathways An interesting observation in this



FIG 195 —*a* The three standard leads Pre-excitation syndrome during normal rhythm

case was that exercise improved the conduction in the A V bundle not only for the sinus beats but also for the extrasystoles

Fig 195 was obtained from a fifty eight year old man complaining of attacks of

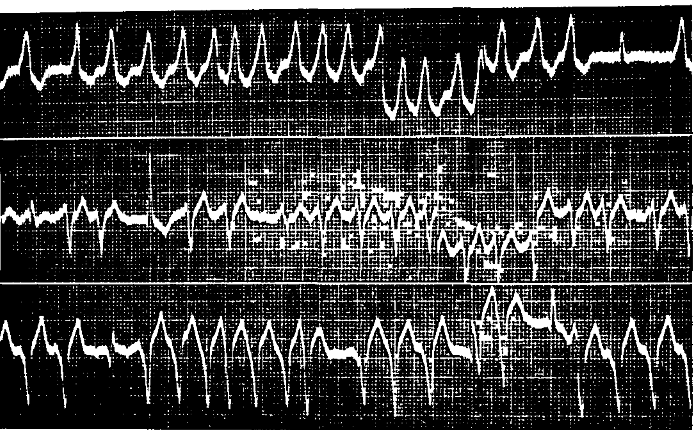


FIG 195 — *b* From the same patient as Fig 195—*a* The 3 standard leads During an attack of auricular fibrillation For further explanation see text

palpitation lasting from a few minutes to several hours The tracings reproduced in Fig 195a indicate the WPW syndrome in lead 1 the characteristic broad slurring in the ascending limb of the R waves is easily recognized Fig 195b was obtained from the same patient during an attack of auricular fibrillation *It is evident that most of the beats show anomalous* intraventricular conduction though a few (the penultimate in lead 1 the fourth in lead 2 and two in lead 3) have ventricular complexes indicating normal A V conduction but are other wise abnormal due to myocardial damage caused by coronary sclerosis Those beats which show evidence of being conducted through an accessory pathway have continually varying form of the QRS complexes the width of which varies between 0 10 and 0 14 second Combination beats also occurred The assumption follows that both the normal A V and the accessory bundle were functioning and that some of the impulses reached the ventricle through both pathways

Recognition of this syndrome is also important because of the possible confusion in some cases with extrasystoles Fig 196 provides an example It shows sinus rhythm where by every other beat shows the pre excitation syndrome Casual inspection may suggest bigeminal rhythm with ventricular extrasystoles occurring late in diastole whereas the correct explanation is regular sinus rhythm with alternation of ventricular excitation be tween normal and anomalous intraventricular conduction (*see also* chapter on Coup ling Fig 136)



Fig 196—Sinus rhythm with every other beat showing the pre excitation syndrome *See* text

Underlying Mechanism

The most generally accepted explanation of the syndrome of shortened P R intervals with anomalous intraventricular conduction is that put forward by Holzmann and Scherf in 1932 and Wolferth and Wood in 1933 According to this view the impulse originates normally in the S A node but is conducted to the ventricles by an abnormal pathway particularly but not invariably the right lateral bundle described by Kent in 1892 and often called the bundle of Kent Several such connexions have been described and some of them were found in patients who had shown the WPW syndrome (for instance Wood Wolferth and Geckeler Oehnell) Scherf and Schönbrunner pointed out the phylo genetic significance of such accessory pathways as remnants in man of the more numerous and broader connexions found in lower animals

Numerous other explanations were put forward at different times by different investi gators they are listed in the paper by Hunter *et al* Of these Holzmann and Scherf con sidered but rejected the assumption of an irritable focus in the ventricle which in such cases is stimulated mechanically by each auricular contraction This view has recently been tentatively put forward again by Kossmann *et al* In recording intracavitary leads these authors found the temporary occurrence of pre excitation complexes on slowly withdrawing the catheter from the right ventricle and suggest that this procedure created an irritable focus in the right ventricular endocardium probably septum which was stimu lated by the auricular contraction possibly by the slight rise in intraventricular pressure which it causes They thus suggest tentatively a functional rather than an anatomical

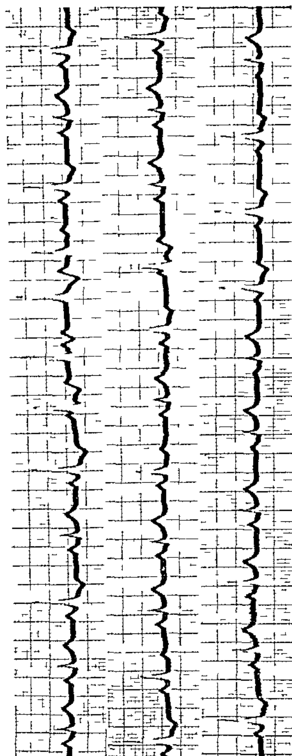


FIG 197.—Arrhythmia recorded during cardiac catheterization in a forty two year old man with congenital pulmonary stenosis Ventricular ectopic beats at times simulating pre excitation complexes The three strips are continuous For further explanation see text

explanation of this syndrome Coelho *et al* arrived at similar views as a result of clinical and experimental observations

While on the grounds of personal observations we can confirm the occurrence of pre excitation complexes during cardiac catheterization (*see* Fig 197) we do not believe that this indicates the creation of an irritable focus in the ventricles activated by auricular contraction but consider such beats to be ventricular ectopic beats elicited by the catheter the timing of which results in the fortuitous appearance of pre excitation complexes Such timing is the more easily understandable as some varieties of ectopic ventricular rhythms are known to have rates very similar to that of the prevailing sinus rate For instance the rates of ectopic ventricular rhythms elicited in dogs by mechanical stimuli parallel those of the sinus rhythm in the individual case (Scherf 1926) and a similar parallelism between ectopic and sinus rates was demonstrated in experimental parasystole (Scherf and Chick) (Comparable conditions were found by Luten in a case with auricular extrasystoles discussed on p 260) Moreover more recent observations in two cases have shown unquestionable disturbances of atrio ventricular conduction in the presence of the pre excitation syndrome which in our opinion proves that this phenomenon is in fact due to anomalous conduction (Scherf Blumenfeld and Mueller)

An interesting problem is the high incidence of paroxysmal tachycardia in such cases Hunter *et al* found the WPW syndrome in 5 per cent of 150 consecutive patients with paroxysmal tachycardia other figures were given earlier in this section The association is certainly not fortuitous and requires an explanation

One theory goes back to the hypothesis of Mines (1914) and de Boer (1927) put forward at a time when the pre excitation syndrome was not yet recognized this seeks to explain extrasystoles and paroxysmal tachycardia as due to a circus movement involving the A V conduction system and the bundle of Kent According to this view the impulse is conducted through the A V system from the auricles to ventricles and thence back to the auricles through the bundle of Kent A circus movement through this pathway was assumed to underlie supraventricular tachycardia Circulation of the excitation in the reverse direction through the same paths was thought to precipitate ventricular tachycardia It is true that in experiments on dogs and cats Butterworth and Poindexter were able to produce paroxysmal tachycardia by stimulating the auricle by means of the amplified ventricular action current However the objection to this explanation is that sharply inverted P waves should be found between two ventricular complexes in leads 2 and 3 and no such instance has so far been published Moreover the observation that in a case of WPW syndrome during auricular paroxysmal tachycardia the excitation was found to use either pathway at different times is not in accordance with the assumption of a circus movement (Scherf and Boyd)

Another explanation seems more plausible put forward by Scherf (1950) It is based on the observation that an excitation activating the heart late in systole or early in diastole that is during the critical or vulnerable phase may precipitate a series of contractions a repetitive response instead of one single contraction (*see* p 483) It seems possible that in patients with the pre excitation syndrome the excitation which reached the ventricle through one pathway arrives by the other pathway in the auricle during its critical phase and in this way causes a repetitive response in the form of paroxysmal tachycardia or auricular fibrillation

SUMMARY

The Wolff Parkinson White or pre excitation syndrome is characterized in the electrocardiogram by abnormally short P R intervals and anomalous intraventricular conduction In this condition extrasystoles are commoner than the few published examples may suggest Several instances are given and illustrated

Activation of the ventricles by an accessory A V connexion is the explanation most

generally accepted A functional explanation—previously rejected—based on the assumption of an irritable focus in a ventricle which is activated by the auricular contraction has recently again been put forward on the grounds of observations made during the recording of intracavitary leads Reasons are given why we consider this view to be unacceptable

The difficulties in the differential diagnosis in some cases between the WPW syndrome and ventricular extrasystoles are emphasized

The association of the WPW syndrome with paroxysmal tachycardia is universally recognized The explanation is put forward that this may be due to the return of the impulse from the ventricles to the auricles during the vulnerable phase of late systole or early diastole of the auricles thereby resulting in repetitive response

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EXTRASYSTOLES IN RELATION TO VARIOUS TYPES OF EXTRACARDIAC CONDITIONS

Cheyne Stokes

In patients with Cheyne Stokes breathing arrhythmias of various kinds are sometimes observed amongst them extrasystoles which periodically occur only during certain phases of this periodic type of respiration

In two digitalized patients extrasystoles were noted during the hyperpnoeic phase (Roth)

In Fischer s case ventricular extrasystoles occurred at the end of hyperpnoea and Wassermann reported tachycardias with ventricular extrasystoles during apnoea Extrasystoles occurring during certain phases of the respiratory cycle were also reported by Wenckebach and Winterberg and by Hoesslin

Fig 198 was obtained from a sixty seven year old woman with marked Cheyne Stokes breathing she had not received digitalis On clinical examination tachycardia was noticed during the apnoeic periods which the electrocardiogram revealed to be an ectopic ventricular tachycardia starting soon after the beginning of apnoea and extending into the beginning of the hyperpnoeic phase Alternation of the ventricular complexes was often seen during the ventricular tachycardia (*see* top tracing Fig 198)

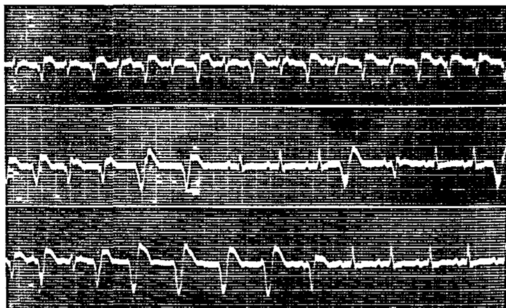


FIG 198 —All records lead 2 Change of rhythm during the various phases of Cheyne Stokes breathing Ectopic ventricular tachycardia starting soon after the beginning of apnoea Note alternation of ventricular complexes Sinus rhythm at the beginning of dyspnoea

Regarding the underlying mechanism of such periodically recurring arrhythmias the periodical changes in the gaseous composition of the blood seem to be the most important factor It may be recalled that a rise in the carbon dioxide content of the blood inhibits the formation of extrasystoles (Scherf Goldenberg and Rothberger) and may transform an ectopic tachycardia into single extrasystoles (*see* sections on Coronary Disease and on Digitalis) This aspect was studied by Steele and Anthony in respect of Cheyne Stokes respiration As expected the lowest concentration of O_2 was found during the early stages of the hyperpnoeic phase the highest at the end of hyperpnoea or beginning of apnoea regarding the concentration of CO_2 the reverse changes were observed The patient investigated by these authors showed arrhythmias of various kinds including paroxysmal tachycardia during apnoea and varyform ventricular extrasystoles at the transition from apnoea to dyspnoea

In addition to changes in the gaseous composition of the blood those in rate and in nervous tone seem important contributory factors

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Hyperventilation

As far as we are aware the effect upon ectopic impulse formation of hyperventilation and alcalosis has not been investigated One personal observation may briefly be discussed in which hyperventilation was repeatedly followed by a conspicuous reduction in the number of ectopic beats

The patient in question was kept under observation for many years and electrocardio grams invariably showed long paroxysms of ectopic auricular tachycardia As the P waves were inverted in leads 2 and 3 the abnormal beats presumably originated in the vicinity of the coronary sinus (*see* Fig 199) When the P wave occurred early in diastole being super imposed on the preceding T wave the P R intervals were usually slightly prolonged Fol lowing hyperventilation of five minutes either bigeminal rhythm was observed (Fig 199b) or two normal beats were followed by an auricular extrasystole (Fig 199c) or a trigeminal rhythm ensued with marked aberration of intraventricular conduction (Fig 199d) A few minutes after the termination of hyperventilation the arrhythmia reverted to the original ectopic tachycardia as reproduced in Fig 199a In this particular patient bi or trigeminal rhythms were never observed except after hyperventilation

X ray Irradiation

In view of the profound effect of X rays on living tissue some influence on ectopic im pulse formation is only to be expected but in actual clinical experience is far less common than anticipated

In 1897 Segny and Quenisset reported intolerable palpitation and irregular contractions as a result of very long X ray irradiation Some arrhythmias not further analysed were reported by Coutard and Lavedan in these extrasystoles may have played a part

In rabbits ventricular extrasystoles were observed two hours after irradiation of the prae cordial area (Gordon Strong and Emory) But as in rabbits extrasystoles are very fre quently observed generally and are easily elicited by a great variety of circumstances such findings are to be accepted with considerable reserve In this connexion it is significant that in dogs paroxysmal tachycardia and auricular fibrillation were observed after irradiation of the praecordial region (Hartman Bolliger Doub and Smith) In man extrasystoles are only rarely encountered in such circumstances (Leach 1943b) and we are not aware of any proved instances This is rather remarkable in view of the severe damage to the myocardium

(Hartman *et al* Warthin and Pohle Werthemann Desjardins) also the clinical observation of pericarditis resulting from this interference (Leach 1943a) Greater resistance to the damaging effect of the X rays of the heart than of the lungs was claimed by Desjardins and it

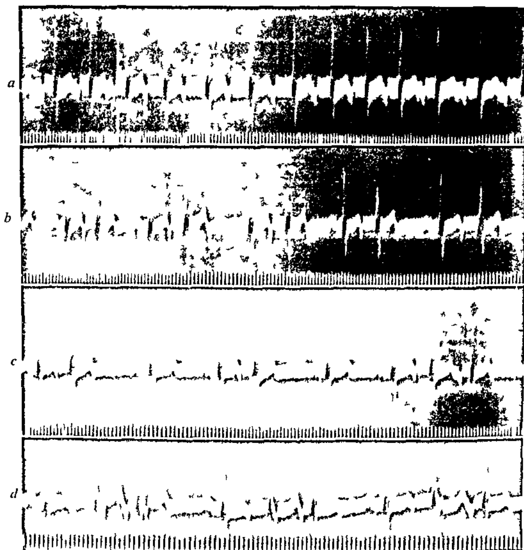


FIG 199—Lead 2 *a* Before hyperventilation Ectopic tachycardia presumably originating in the vicinity of the coronary sinus Note sharply inverted P waves *b* *c* and *d* after five minutes hyperventilation *b* Bigeminal rhythm *c* Two normal beats followed by an auricular extrasystole Two auricular extrasystoles in succession at the end of this strip *d* Auricular trigeminy with aberrant intra ventricular conduction of the extrasystoles Time base 0 04 second

is noteworthy how often irradiation with large doses is given for mediastinal tumour without much clinical evidence of myocardial damage In the electrocardiogram signs of myocardial damage are by no means rare and gallop rhythm may appear in such circumstances (unpublished personal observations) these features have to be ascribed to the X ray treatment

(Gendreau claimed to have found far reaching effects of X rays on the heart but his electrocardiograms show only artifacts)

Regarding extrasystoles our personal experience is limited to one case It concerned a patient with short paroxysms of auricular tachycardia which were separated by only one sinus beat (extrasystolie a paroxysmes tachycardiques p 237) (Fig 200a) This arrhythmia was invariably recorded during a period of observation extending over many years About four hours after irradiation of the praecordial region with 100R the arrhythmia reproduced in Fig 200b was found the chains of ectopic beats had become shorter and two sinus beats followed in succession the last of the auricular ectopic beats was blocked The same effect upon the arrhythmia was repeatedly observed also when other parts of the body were irradiated It seems reasonable to conclude that this change in the arrhythmia was due not to any direct effect upon the heart but to an indirect effect consisting most probably in a metabolic change resulting from the irradiation

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Hyper and Hypothyroidism

Hyperthyroidism

In view of the common occurrence in hyperthyroidism of auricular fibrillation it is surprising that extrasystoles are comparatively rare (Wilson) This is the more remarkable since in other conditions predisposing to auricular fibrillation (coronary disease mitral stenosis) auricular extrasystoles are found so often as precursors The increased heart rate was considered to be one factor to account for the comparative rarity of extrasystoles in this condition (Bickel and Frommel Wishart) and if extrasystoles were found in such cases in spite of a high heart rate they were thought to indicate myocardial damage (Boas and Levy) Towers considered the occurrence of extrasystoles in the presence of sinus tachycardia as typical for hyperthyroidism How infrequent extrasystoles are in hyperthyroidism may be illustrated by recalling Goodall s review of the heart in Graves disease in which 7 per cent of the patients were found to have auricular fibrillation and extrasystoles were not mentioned at all Similar findings were reported by Willius

On the other hand five instances of ventricular and three of auricular extrasystoles were encountered amongst 188 patients with hyperthyroidism (Parade) and Van de Velde especially stressed an incidence of 4 per cent in his series of five hundred cases Other studies include those of Bickel and Frommel (three instances amongst eighty cases) and of Krumbhaar (three amongst forty seven) It appears that ventricular extrasystoles are commoner than auricular ones (Nicholson)—another surprising observation This is also borne out

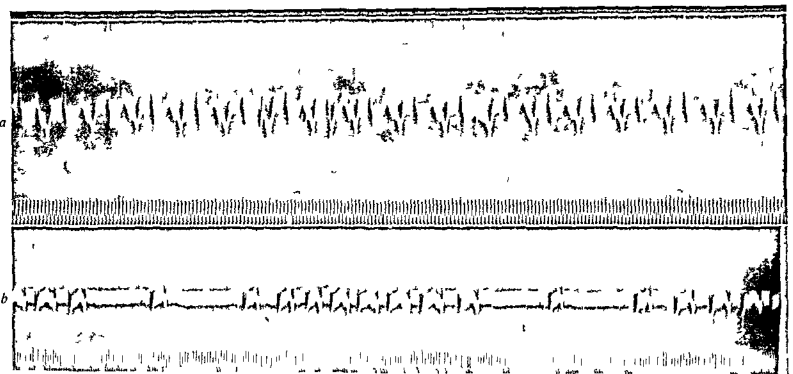


FIG 200.—Top record Before irradiation Paroxysmal auricular tachycardia The paroxysms are fairly long and separated by only one sinus beat (Extrasystolie à paroxysmes tachycardiques.) Bottom record Four hours after irradiation of the precordial region with 100 R Shorter paroxysms of ectopic tachycardia two sinus beats in succession blocked auricular extrasystoles Time base 0 04 second

by the figures of Spang and Korth of the twenty four patients with extrasystoles amongst two hundred cases of hyperthyroidism fifteen had ventricular and one ventricular and auricular ones

Experimental investigations do not seem to throw any light on this problem Bickel and Frommel observed ventricular extrasystoles in rabbits which had been injected with extracts of thyroid glands of sheep But since such ectopic beats occurred very soon after the injec tion sometimes within a few seconds and in any case rabbits are very prone to exhibit such arrhythmias this observation is of doubtful value

It has to be admitted that neither the rarity of extrasystoles nor their predominantly ventricular origin is understood As the reason for the frequent occurrence in hyperthy roidism of auricular fibrillation is not clear this is hardly surprising There can be no doubt that the association between auricular fibrillation and hyperthyroidism is more than for tuitous Increased sympathetic tone has been thought to be responsible for this connexion but this is far from certain On the contrary there is some evidence that increase in para sympathetic tone may play a part administration of choline preparations to patients with hyperthyroidism causes auricular fibrillation more readily than that to normal subjects (Nahum and Hoff) There is also evidence of a direct action of the thyroid hormone on the heart muscle fibres

Hypothyroidism

In our experience the occurrence of extrasystoles in patients with hypothyroidism is not rare but it seems doubtful whether this clinical condition predisposes to extrasystoles In ong standing cases they are caused by the associated coronary sclerosis

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Extrasystoles and Different Phases of Sexual Life in Women

The relationship between the occurrence of extrasystoles and the different phases in the sexual life of women has been noticed for a very long time In the pre electrocardiographic era the utero ovarian arrhythmias were a well recognized group of irregular heart action Early such arrhythmias attracted attention particularly amongst French clinicians who were inclined to attribute them to reflexes (Leconte Marchal and Heim de Balsac Gallavardin)

While such reflexes may perhaps play a part in some cases it is certain that endocrine factors are usually responsible With increasing endocrinological knowledge it became realized that imbalance between the various endocrine glands rather than ovarian hypo or hyper function had to be considered as the main underlying factor acting most probably via alteration of the electrolyte balance

The greater incidence of extrasystoles in women as found in some statistics (*see* section on Incidence) was attributed to arrhythmias of such etiology (Savini)

Pregnancy predisposes to extrasystoles to such an extent that not infrequently this is the only time in a patient s life when they occur (Mackenzie 1902) and it has been estimated that as many as 50 per cent of pregnant women show extrasystoles (Mackenzie 1921) As *a rule they occur during the later months of pregnancy about the eighth month and dis* appear within a few hours after delivery (Mosler and Sachs Goodall Schubert Jensen Abraham Hoskin) Origin by way of reflex is also likely to be an important factor But great variations are found in different cases and in some women who develop extrasystoles only during menstruation they may be absent throughout the whole of pregnancy In others paroxysmal tachycardia is observed during pregnancy (Weyler and Dustin) Anderson (1933) followed up a patient during successive gestations and found that during the first three pregnancies no attacks occurred three attacks of paroxysmal tachycardia were seen during the fourth one during the fifth (in the eighth month) three in the sixth and more numerous ones during the seventh pregnancy when they started already in the course of the fifth month no attacks were een between the pregnancies An unusual observation was reported by McMillan and Bellet namely attacks of ventricular paroxysmal tachycardia occurring during pregnancy for the first time and persisting afterwards

The treatment of extrasystoles occurring during pregnancy—which may be very trouble some—pre ents a special difficulty since small doses of quinidine often are ineffective and large ones contra indicated Fortunately reassurance about the harmless and transient nature of the arrhythmia often is all that is required

Menstruation Menopause and Puberty

Ectopic arrhythmias may occur only during menstruation (Crawford Sigler and Fruchter) or just before it In others extrasystoles and paroxysmal tachycardia were recorded during the menopause (Hoffmann Peel Anderson 1932) In such cases it is often impossible to be certain whether extrasystoles had not existed before and were only noticed by the patients during the menopause when the change in their general condition makes patients more prone to notice such disturbances of rhythm

Disappearance of extrasystoles with the onset of puberty has also been reported (Anderson 1933)

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Allergy

Experimental Investigations

In dogs made anaphylactic by the intravenous injection of horse serum extrasystoles were not observed though heart block occurred (Auer and Robinson) In rabbits on the other hand in similar conditions extrasystoles including bi and trigeminal rhythms were noted in thirteen out of fifteen experiments (Hecht and Wengraf) They were attributed to muscular spasm in the coronary arteries (Miculicich) Too much attention should not be paid to such observations in rabbits since as mentioned repeatedly rabbits develop extra systoles very readily in a great variety of experimental conditions In guinea pigs extra systoles were seen during attacks of bronchial asthma experimentally produced (Ewert and Kallos) According to Criep arrhythmias seen in rabbits and guinea pigs during anaphy lactic conditions are due to the concomitant asphyxia since artificial asphyxia produced the same kind of arrhythmias as did anaphylaxis

Clinical Observations

Extrasystolic arrhythmias were reported in patients allergic to a great variety of agents sweet food (Luria and Wilensky) cold (Duke) a variety of foodstuffs (Weill Lapeyre Harkavy Pantolini) Such arrhythmias included single extrasystoles and paroxysms of ventricular tachycardia In view of the profound tissue—in particular vascular—changes caused by allergy the occurrence of extrasystoles in such conditions is easily understood

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Emotional Factors

Changes of the pulse due to emotions were known to Galen The following charming anecdote of which Avicenna (980–1037) the famous Arabian physician is the hero may be quoted from E G Browne s Fitzpatrick Lectures

When in his flight from Mahmud of Ghazna he came incognito to Jurjân or Gurgâr (the ancient Hyrcania) by the Caspian Sea a relative of the ruler of that province lay sick of a malady which baffled all the local doctors Avicenna though his identity was then unknown was invited to give his opinion and after examining the patient requested the collaboration of someone who knew all the districts and towns of the province and who repeated their names while Avicenna kept his finger on the patient s pulse At the mention of a certain town he felt a flutter in the pulse Now said he I need someone who knows all the houses streets and quarters of this town Again when a certain street was mentioned the same phenomenon was repeated and once again when the names of the inhabitants of a certain household were enumerated Then Avicenna said It is finished This lad is in love with such and such a girl who lives in such and such a house in such and such a street in such and such a quarter of such and such a town and the girl s face is the patient s cure So the marriage was solemnized at a *fortunate hour chosen by Avicenna and thus* the cure was completed

The list of emotions reported to cause extrasystoles is long It includes anxiety fear fright hate to quote a few (Webber Lockwood Bickel Katz *et al*) domestic or professional troubles disappointment feeling of guilt or shame and fear of organic heart disease (Wenckebach and Winterberg p 242)

Fleisch recorded extrasystoles in two thirds of subjects investigated during an examination and Miller and McLean described four instances of extrasystoles occurring during severe inner conflicts Gallavardin and particularly Hoffmann reported attacks of paroxysmal tachycardia regularly elicited by emotion and Ken Kure saw multiple extrasystoles and tachycardias in a patient whenever he was asked to solve simple mathematical problems

That emotions may precipitate extrasystoles becomes understandable if the effect of epinephrine and acetylcholine and the part played by the hypothalamic centres and by autonomic nerves and reflexes is recalled these are discussed in the appropriate chapters

In view of the fact that premature contractions occurring during a certain period in early diastole (the critical or vulnerable period *see* p 483) may initiate ventricular fibrillation sudden death caused by sudden great fright becomes understandable some instances are briefly discussed by Wenckebach and Winterberg (p 511)

There is moreover a further relationship between emotion and extrasystoles namely the arrhythmia causing anxiety and apprehension To most laypeople any irregularity of the heart s action spells heart disease and once the patient s attention is focused on the missed beats the increasing anxiety about his discovery is an important factor in increasing the number of extrasystoles (*see* also section on Symptoms) Thus in some instances it is difficult to decide whether anxiety or extrasystoles are the primary disturbance If Stevenson *et al* found anxiety patterns in eleven out of twelve unselected subjects with extrasystoles doubts may be entertained whether such series consisted in fact of unselected individuals

The reverse phenomenon is also observed namely the disappearance of extrasystoles due to emotion (Robinson and Draper) The commonest experience is the absence of extrasystoles on examination of patients whose history makes the presence of premature beats most probable and in whom they can be brought out by certain measures (exercise amyl nitrite) In such cases the emotional strain invariably associated with a medical examination particularly by a strange doctor temporarily abolished the arrhythmia (*see also* section

on Incidence) Moreover a large proportion of patients with anxiety state have a normal heart rhythm though often an increased rate This is in keeping with the observation that in certain experimental circumstances stimulation of the cardiac sympathetic nerve or the administration of epinephrine abolished ectopic arrhythmias Clinically the conclusion seems warranted that the causation by emotions of extrasystoles is dependent on a certain *milieu intérieur* the peculiarities of which are little known

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Miscellaneous Clinical Conditions

Infectious Diseases

Since myocarditis is often a feature of the most diverse kinds of infections (coccal virus bacillary protozoal) (Scherf and Boyd Saphir) it is easily understood that extrasystoles occur frequently in their course With the exception of diphtheria in which the primary cardiac lesion is degenerative with reactive inflammatory changes no systematic investigations are available about the rate of incidence and the various types of extrasystoles in individual infections and no useful purpose would be served by undertaking such studies Brief references to some papers on this subject may however not be amiss

In view of the frequent involvement of the myocardium in *diphtheria* extrasystoles should be expected to occur frequently in this disease but reports about their incidence vary considerably

The great discrepancies become evident by comparing the papers of Seckel and of Shookhoff and Taran (1931b) whereas the former reported extrasystoles in thirty four out of seventy five cases of diphtheria (45 per cent)—only ten of these patients showing clinical evidence of myocardial involvement—the latter found only one instance of (auricular) extrasystoles in fifty patients In a series of ninety cases Marvin found only two instances of auricular and one of ventricular extrasystoles Such differences may at least partly be due to the method of examination thus a longer rest before examination a prolonged period of observation an investigation carried out by a physician who is familiar to the child all this may result in a lower heart rate and thereby in the occurrence of more numerous extrasystoles

A high incidence was also reported by Stienon Other investigators report figures round about 20 per cent for example Gunson twenty eight instances amongst 120 patients (23 per cent) in whom extrasystoles occurred between the ninth and sixty sixth day Smith 20 per cent of 242 cases

Disagreement also exists about the most frequent site of origin of extrasystoles in diphtheria predominance of auricular extrasystoles was found by Gunson and by Koppang of ventricular ones by Begg and by Smith We are in agreement with the latter view Occcasionally multiform extrasystoles and even short bouts of paroxysmal tachycardia with alternating ventricular complexes were reported (Stecher)

Gunson s statement that the occurrence of extrasystoles in diphtheria was of no material prognostic significance and did not indicate the necessity of bed rest is not acceptable to us Actually Hume pointed out long ago that in this condition extrasystoles may occasionally be the first sign of myocardial involvement

In *lobar pneumonia* extrasystoles were described by de Graff Travell and Yager Mackenzie (1902) considered them to be an ominous sign but modified this statement in his later writings Extrasystoles were described in *scarlet fever* by Kiss and Romhanyi but thought to be rare in this condition by Shookhoff and Taran (1931a) In *bacterial endocarditis* they were seen in 7 per cent by Segal Chagas and Villela described a cardiac form of *trypanosomiasis* with many ventricular and also auricular extrasystoles this was confirmed by Arrillaga Soldati and Gandulla

Rheumatic fever

In this condition extrasystoles were described as a common occurrence (Peel) they were seen in 25 per cent of the cases (Campbell) Their occurrence is considered to indicate active myocarditis

Scorpion s bite

An observation of tachycardia with extrasystoles caused by scorpion s bite has been reported by Celoria and Sloer

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EXTRASYSTOLES AND LIFE INSURANCE

In the assessment of proposals for Life Insurance the finding of extrasystoles is an important factor While with some companies their presence alone appears to preclude acceptance at the normal premium even in the absence of any other pathological finding (Salvesen) a more scientific and discriminating approach prevails with others and every case tends to be judged on its own merits

In order to obtain some information about the attitude taken by Insurance Companies towards applicants who have extrasystoles but are otherwise healthy we directed an inquiry about this to fifteen of the leading Life Insurance Companies of the United States and Great Britain We received informative and often detailed replies for which we should like to express our appreciation to the companies concerned

Two points were emphasized in many of such replies The fact that each application is considered individually and the practice to accept applicants as good average (first class) lives if they are healthy in every other respect

Individual companies vary regarding particular points to which they attach special importance These are summarized in Table 5 in which such factors are marked by + It is based on the more detailed replies which we received from eleven companies

TABLE 5

Company	Number of es per minute	Runs of es	Age of patient	Persistency of es	Rate of basic rhythm	Appearance or disappearance after exertion	Multiform es	Changes in T waves of post extrasystolic beat
1	+		–					
2	+	–			+	+	+	
3	+		+			+		
4	+					+		
5		+	+				+	+
6	+		+			+		
7				+				
8	+		+	+				
9	+					+		
10			+					
11	+		+		+			

es = extrasystoles

The table shows that most companies pay much attention to the number of extrasystoles per minute According to one more than eleven extrasystoles per minute indicates a substantial increase in risk Another holds that the risk increases with age and with increase in the number of persistently intermittent pulses This company instances an example that at the age of fifty six with an intermittent pulse of under five per minute a mortality of 80 per cent in excess of the normal should be expected with five to ten per minute the expected mortality should be regarded as twice the normal The same Company attached an extract from a book written by Dingman on the subject of Risk Appraisal in which the effect on the mortality ratio of pulse intermittence is detailed This extract shows that such pulse intermittency comprised extrasystoles and dropped beats between which no distinction seems to have been made An approach which does not distinguish between these basically different kinds of arrhythmias seems to us highly questionable

In our opinion the number of extrasystoles alone cannot be held to be a valid criterion regarding life expectation Since we consider true extrasystoles to be due to an abnormality in one circumscribed focus (*see* chapter on Mechanism) and such an ectopic centre to consist of a very small number of cells—perhaps only one cell—it will depend solely on the degree of the abnormality in such a small area whether one extrasystole will occur per minute or many Thus even if one extrasystole follows each normal beat and bigeminal rhythm prevails such an arrhythmia does not denote that the individual should be regarded as a more serious risk than those who have only three or five premature beats per minute

Even if short runs of extrasystoles occur the importance of which was stressed by two companies the heart often is normal in every other respect as it actually is in the majority of individuals with supraventricular paroxysmal tachycardia We agree however, that in such instances the case should be treated individually and with special caution as in the *event of auricular extrasystoles there is an increased probability of auricular fibrillation* occurring

Another point to which great importance is attached by several companies is the age at which extrasystoles occur or are found In our opinion this is fully justified since in individuals over forty premature beats may be an early sign of coronary disease One company disregards extrasystoles in applicants under forty but in those over forty an extra premium is asked for Other companies draw the line at forty five beyond which they request a moderate increase in premium

A further point stressed by two companies is the persistency of the extrasystolic arrhythmias Thus one company accepts such applicants only at an additional premium The evidence available about persistent premature beats does not appear conclusive for forming an opinion whether this attitude has a foundation in fact and it seems to us that in such *cases individual assessment is of particular importance*

We would advocate the same attitude regarding extrasystoles occurring with sinus rhythm of higher rates Here the length of coupling is a decisive factor extrasystoles with short coupling that is occurring early in diastole may and do occur in tachycardia whereas those with longer coupling require a diastolic period of greater length to become manifest and therefore are seen only with slower rates As there is no reason to attach a prognostic significance to the length of coupling it seems highly dubious in applicants with extrasystoles to expect a higher mortality in those with a faster S A rhythm (Berliner and Huppert)

We concur with the view that extrasystoles occurring during or shortly after exercise as well as multiform ones preclude acceptance of the applicants as normal risks The former often and the latter invariably indicate organic heart disease as is discussed in the appropriate sections (*see* pp 416 and 144)

The significance of alterations in the T wave of the first post extrasystolic beat which was mentioned in the reply of one company is discussed on p 37

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INCIDENCE OF EXTRASYSTOLES

Introductory Remarks

There seems hardly a human being who at one time or another has not had extrasystoles They may be and often are accidentally found during a medical examination the subject being quite unaware of their presence The reverse is equally common some symptoms entirely due to extrasystoles made the patient seek medical advice but none are found on examination Some emotional tension inevitably caused by the investigation abolished all arrhythmia during the crucial half hour or so of the examination via changes in autonomic nervous tone often some slight increase in rate occurs which shortens the diastolic phase For these reasons statistics about the frequency of extrasystoles have a very limited value In order to be reliable regarding diagnosis they should be based on graphic records preferably electrocardiograms otherwise they will be almost valueless for demonstrating the true incidence amongst the general population Even regarding the frequency with which extrasystoles occur amongst patients hospital or private wide differences in the figures have to be expected because of the inevitable selection of cases for such an investigation Thus the incidence will vary according to whether such statistical studies are undertaken in a general hospital or in a cardiac department in a more general private practice or in one with predominantly cardiac patients whether regarding age groups a cross section of the whole population is examined or the study is based on the older age groups in which coronary sclerosis forms a significant predisposing factor rendered even more important by the exhibition of digitalis particularly if this drug is given in larger doses A cardiologist will see more cases with extrasystoles than a general physician

With these reservations a few statistical investigations may be quoted in order to convey some general impression about the frequency with which extrasystoles have been encountered in different circumstances

General Incidence

Amongst 5 124 males examined for life insurance extrasystoles were found in 194 that is 3 8 per cent (Leslie) In a group of 500 recruits for the Royal Canadian Air Force the incidence of extrasystoles was twelve that is 2 4 per cent (Stewart and Manning) and in one of 1 000 aviators of the American Air Force fifteen (1 5 per cent) (Graybiel *et el*)

Passing from these sections of the general population to hospital patients generally and cardiac patients in particular a higher incidence of extrasystoles tends to be encountered Some relevant data are summarized in Table 6 The wide variations in these statistics are evident

Incidence of Extrasystoles in Subjects with Normal and Abnormal Cardiac Conditions

To what extent does the occurrence of extrasystoles indicate a pathological cardiac condition? Does the incidence of extrasystoles in normal subjects and in cardiac patients as revealed in investigations on larger series provide any reliable evidence about this problem? The answer unfortunately is in the negative the figures in different investigations (*see* Table 7) vary to such an extent that nothing but a general impression is obtained

TABLE 6

INCIDENCE OF EXTRASYSTOLES AMONGST HOSPITAL PATIENTS GENERALLY AND CARDIAC PATIENTS

Number of Patients examined	Number of Extra systoles	Per cent	Remarks	Author
10 000	1 503	15	Patients electrocardiographed 1914–1931 at Massa chusetts General Hospital	White 1944
25 000	3 034	12	Patients electrocardiographed 1934–1943 at Massa chusetts General Hospital	White 1944
16 810	—	1	Patients electrocardiographed 1940–1942 at Metro-politan Hospital New York Electrocardiograms are taken routinely	Scherf
12 473	286	2 3	General Hospital medical cases	Laake
6 000	270	4 5	—	Unghváry
2 500	—	ca 70	Patients examined for cardiac complaints Extra systoles either deduced from history or present on examination	Holzmann
500	—	ca 20	Consecutive series referred to a Cardiographic Depart ment	Campbell

TABLE 7

INCIDENCE IN PER CENT AMONGST CASES WITH EXTRASYSTOLES OF PATIENTS WITHOUT ANY EVIDENCE OF ANY OTHER CARDIAC ABNORMALITY

Number of patients with extra systoles	Incidence in per cent of patients with out any evi dence of any other cardiac abnormality	Remarks	Author
1 142	54	Examination for Life Insurance	Ungerleider and Gubner
194	34 2	Examination for Life Insurance 34 2 per cent with evidence of heart disease 31 6 per cent borderline cases	Leslie
100	55	Consecutive cases in a naval hospital	White 1927
278	55	—	Wenckebach and Winterberg
184	32 5	—	Peel
231	46 8	Patients aged 75–96	Willius
216	7	Hospital patients 81 5 per cent had evidence of heart disease 11 5 per cent were suspect of heart disease	Unghváry

A reasonable estimate seems to be that in 30–50 per cent of hospital patients with extra-systoles the cardio vascular system is otherwise normal This proportion is much larger in patients seen in private practice Contrariwise the incidence of extrasystoles in patients with coronary sclerosis is considerably greater than in the general population and further enhanced if digitalis is given This also accounts for the more frequent occurrence of extra systoles in old age (*see* below) Similarly certain infections predispose to premature beats for example diphtheria and auricular extrasystoles are common in rheumatic mitral lesions often preceding auricular flutter or fibrillation Amongst patients suffering from such con-ditions the incidence of premature beats will be far higher than in the general population

Incidence of Different Types of Extrasystoles

Table 8 shows the distribution of extrasystoles according to their site of origin It will be seen that on the whole the figures of the several authors are in satisfactory agreement Auricular extrasystoles are much less common than ventricular ones the incidence of the former being on an average about half that of the latter

TABLE 8
DISTRIBUTION OF EXTRASYSTOLES ACCORDING TO THEIR SITE OF ORIGIN

Number of Tracgs exam d	Numb r of Extra systol	Per cent	Ventr	Per cent	Supra ven tric	Ventr and Supra ventric	Remarks	Author
1 000	15	1 5	8	53	7	0	Young healthy aviators	Graybiel *et al*
500	12	2 4	9	77	3	0	Young healthy aviators	Stewart *et al*
10 000	1 503	15 5	974	65	529	0	Patients in general hospital	White 1944
25 000	3 304	12 1	2 007	66	1 027	0	Patients in general hospital	White 1944
12 473	286	2 3	181	64	105		Patients in general hospital	Laake
6 000	216	3 6	98	45	57	61	Hospital patients	Unghváry
3 769	251	6 8	167	67	84		Only cases without organic heart disease	Nathan
?	194		120		61	6	Only cases with extrasystoles examined In 7 cases origin undetermined	Leslie
500	114	22 8	70	61	44		Patients of a Cardiographic Department	Campbell
5 600	86	1 5	52	60			Children under 16 attending cardiac clinic	Landtman
?	1 142		758	66	384	0	Only cases with extrasystoles examined	Ungerleider and Gubner
24 000	398	1 9	141	62	38	49	Only in 228 cases extra systoles classified	Dauwe
941	160	17 0	74		60		Only patients over 51 In 26 cases origin of extrasystoles undetermined	Martinez
300	38	12 6	15	39	19	4	Ambulatory patients over 60 55 6 per cent were 70–79	Fox *et al*
100	20	20·0	15	75	5	0	Patients over 70	Eliaser and Kondo
315	108	34 2	57	53	51	0	Patients aged 75–96 without cardiac disease	Willius
385	123	31 9	83	68	40	0	Patients aged 75–96 with cardiac disease	Willius
700	231	33·0	140	60	91	0	Total of Willius series	
100	31	31 0	10	32	21	0	Patients aged 80–103 Average age 84 2	Wosika *et al*

One or two common pitfalls in the classification of extrasystoles should briefly be mentioned In many instances the P waves of auricular extrasystoles are buried in the T waves of the preceding beat Unless such a record is carefully analysed the auricular extrasystoles are apt to be misinterpreted either as ventricular ones if the ventricular complexes are abnormal owing to aberrant conduction in the ventricles or as A V nodal ones if the ventricular complexes are of normal shape We believe that the incidence of A V nodal extra systoles as given in some statistics is too high because of the inclusion in this category of

auricular extrasystoles with indistinct or invisible P waves The employment of chest leads with the exploring electrode on the right sternal border or of unipolar limb or oesophageal leads may clarify this distinction In our opinion A V nodal extrasystoles are rare and in all cases in which the differential diagnosis between auricular and A V extrasystoles is in any doubt the term supraventricular extrasystoles should be employed This practice has been adopted in our Table 8

Regarding the incidence of various types of extrasystoles in relation to the cardiac condition of the patient it may be mentioned that in Ungerleider and Gubner s series ventricular premature beats occurred less frequently in cases with cardiovascular disease the figures being 61 and 72 per cent respectively In old people the reverse relationship was found by Willius (*see* Table 8)

Sex

It seems that extrasystoles occur with about equal frequency in the two sexes (Gallavardin Campbell) though some authors report some slight predominance amongst males (Goodall White 1926) The latter found in a series of 1 500 private patients that amongst 103 with extrasystoles and structural heart disease fifty eight were men and forty-five women and a similar sex incidence was found regarding patients with extrasystoles and a normal cardiovascular system Some predominance of males would be understandable *in view of the greater incidence of coronary sclerosis in men but this would be compensated* at least partly by the tendency of extrasystoles to occur during menstruation and pregnancy Laake reported a preponderance of females in each age group

Age

Extrasystoles have been observed at all ages including the foetal heart and at birth

In a study on the incidence of foetal arrhythmias Sontag and Newbery found that extrasystoles appeared about sixty days before birth attained their maximum frequency about one month later then became rarer and disappeared about one week before delivery Their appearance and disappearance was considered related to the stages of development of the autonomic nervous system Hyman considered arrhythmias between the fifth and eighth lunar months as not uncommon opinions about their incidence which he endeavoured to ascertain by means of a questionnaire sent to 100 obstetricians varied widely *namely from 0 to about 25–33 per cent of all cases examined prenatally In a phono*cardiographic study of foetal heart sounds Hyman encountered six instances in which extrasystoles were suspected on the grounds of the phonocardiogram after birth the diagnosis was confirmed when right ventricular premature beats were found In all cases the arrhythmia disappeared within a few days as was also found by Holtermann

Regarding new born infants Hecht reported a case in which blocked auricular extrasystoles were observed for seventeen days after birth but the arrhythmia had already been noticed during delivery Auricular extrasystoles observed in such circumstances may be persistently or occasionally blocked (Antoine Rihl and Weinzierl Fenichel and Kurzrock) or conducted (Barre and Henriet) On clinical examination Lyon and Rauh found extrasystoles in three amongst 5 114 newly born infants (0 06 per cent)

(Burghard and Wunnerlich claimed to have recorded interpolated extrasystoles in ten out of thirty two normal new born infants and Raiha to have found ten instances amongst forty five premature babies examined two to twenty four hours after birth but the reproduced tracings of these authors show only artefacts)

It can be said that extrasystoles in the foetus are not rare that usually they are auricular in origin often blocked and that as a rule they tend to disappear soon after delivery It can also be considered established that premature beats may be present at birth

Some figures about the incidence of premature beats in children are given in Table 9 Several of the authors quoted in this table mention that they have no prognostic significance and they cannot be taken to indicate an abnormal heart (also Leffkowitz) According to Gelman and Brown they increase in frequency at puberty Whether extrasystoles occur more frequently in children with cardiac disease seems uncertain while the figures obtained by Lyon and Rauh in their various series seem to indicate this the figures of the various investigations tabled differ to such an extent that no definite conclusions can be drawn in this respect

TABLE 9
INCIDENCE OF EXTRASYSTOLES IN CHILDREN

Type of Group	Number exam d	Number with Extra systoles	Per cent	Remarks	Author
Normal children	2 672		2 2		Lyon and Rauh
	259	2	0 8		Shookhoff and Taran
	100	1	1		Perry
	100	2	-		Hafkesbring *et al*
Schoolchildren	1 782	40	2 2	Ages under 10 to 19	Lyon and Rauh
Children amongst patients of all ages with extra systoles	226	7	3 1	Ages 10 to 19	Cowan and Ritchie
	100	3	3	up to 14	Smith
Hospital patients generally	1 000	48	4 8	Diagnosis made only by clinical impression	Visco
	400	0	0		Antell
Children attending car diac clinic	5 600	86	1 53	Children under 16 In most cases predisposing factor pres ent e g infection Good pro gnosis Includes 200 normal control	Landtman
	782	35	4 4	Ages 2½–14½	Lyon and Rauh
Children with cardiac disease	100	1	1	Rheumatic heart disease	Drawe *et al*
	100	0	0	Congenital heart disease	Drawe *et al*
	468		4 3		Lyon and Rauh

Regarding middle aged and elderly subjects there can be no doubt that extrasystoles are a very common occurrence (*see* Table 10) Their frequency tends to increase with age as also observed by Laake Generally ventricular origin of the premature beats is com moner than auricular one (*see also* Table 8) The high incidence of extrasystoles in the aged without any other evidence of structural heart disease seems to indicate that even in the oldest they need not have any more serious significance than in the younger person and the figures of Willius quoted in Tables 7 8 and 10 would bear this out

Heredity

Little is known about heredity of extrasystoles An octogenarian cardiac reported in a letter to the *British Medical Journal* that he had had extrasystoles since the age of fourteen and that his father and two sisters had the same condition

TABLE 10

INCIDENCE OF EXTRASYSTOLES IN MIDDLE AND OLD AGE

Age Group	Number examined	Number with Extra systoles	Per cent	Remarks	Author
Over 51	941	160	17	52 per cent aged 51–60	Martinez
Over 60	300	38	12 6	Ambulatory patients	Fox *et al*
60–90	102	9	8 8	Non cardiac patients	Taran and Kaye
Over 70	100	20	20		Eliaser and Kondo
Over 70	100	23	23		Levitt
Over 70	100	28	28		McNamara
75–96	700	231	33	108 without 123 with cardiac disease *See also* Table 8	Willius
80 103	100	31	31	Consecutive cases Average age 84 2	Wosika *et al*

SUMMARY

Reasons are given for the view that all statistical studies about the incidence of extra systoles in the general population have only a very limited value With this reservation some relevant papers are discussed which deal with the incidence of extrasystoles according to the presence or otherwise of cardiac disease site of origin of the premature beats sex and age According to a very approximate estimate in 30–50 per cent of hospital patients with extrasystoles the cardio vascular system is otherwise normal and this proportion is much higher in patients seen in private practice The incidence of auricular extrasystoles is on an average about half that of ventricular ones Premature beats seem to occur with about equal frequency in the two sexes The presence of extrasystoles in the foetus and at birth can be considered as established In middle aged and elderly subjects extrasystoles are a very common occurrence and their incidence tends to increase with age Even in very old subjects their presence need not have any more serious significance than in younger persons In view of the wide variations of the figures in the various series no more definite conclusions about their rate of incidence in the various circumstances can be drawn

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DURATION

Most individuals exhibiting extrasystoles have them only occasionally The premature beats occur singly and sporadically being separated by long periods of normal sinus rhythm There are many who have extrasystoles for only a few minutes or hours and are entirely free from them for many months or years We know of persons in whom they occur only in spring but not during the rest of the year

Extrasystoles may persist for many years in otherwise healthy individuals It is by no means uncommon to be told by a patient that he has had the irregularity ever since I can remember Cases are on record in which extrasystoles were observed for twenty four (de Graff and Batterman) forty six (Esler and White) fifty (Mackenzie) and sixty seven years (Grassmann) Walsh observed ventricular extrasystoles on himself for forty years

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SYMPTOMS

In a great majority of cases extrasystoles do not give rise to any symptoms Even in individuals who have premature beats for a lifetime they may be asymptomatic On the other hand extrasystoles often cause symptoms of greater or lesser severity ranging from an occasional slight momentary discomfort to one of such agony that it becomes frankly disabling

Not infrequently symptoms date from the moment a doctor told the patient that his heart action was irregular or from the patient s accidental discovery of the arrhythmia Once the patient s attention is focused on his heart a vicious circle often starts the patient s observing his heart action more closely resulting in more numerous extrasystoles and vice versa

There is hardly any other cardiac condition of which the patients descriptions vary so much as extrasystoles The word most commonly used is palpitation This term employed by patients to describe many diverse conditions refers in the event of extra systoles not to any sustained or prolonged discomfort but rather to repeated abnormal sensations each of which is isolated and of short duration Further questioning elicits a surprising variety of descriptive terms in different patients Standstill of the heart the heart missing or skipping a beat flapping stammering bumping fluttering stumbling (Homan) tumbling (Mackenzie 1902) slapping bounding against the chest wall (Goodall) faux pas (Bouillaud Huchard) is a small selection Some patients unable to express themselves more distinctly content themselves with reporting a funny feeling (Fahr) Sometimes the description is coloured by analogies to other experiences the patient has had The woman who had borne children might compare the sensation caused by the extrasystole with that of quickening during pregnancy the hunter with that of the quick turn of the hare the athlete with a sudden jump

Sometimes extrasystoles give rise to more unpleasant sensations for instance a feeling of sudden tension or one like the blow of a hammer Other patients complain of a feeling of oppression in the chest (Wenckebach 1898) like having a foreign body in the chest or of fullness in the throat (Leconte) Some French terms for such discomfort are eclair dou loureux baillement avorte and eructation imminente

Occasionally extrasystoles give rise to frank pain (Gallavardin 1929 Wenckebach and Winterberg) This is of very short duration but may be very severe (Wenckebach 1903 1914) In one of our patients it was so intense that it made him jerk his head off the pillow with every extrasystole he compared the sensation with that caused by an electric shock

More general sensations produced by extrasystoles include an indescribable anxiety a sinking sensation a peculiar feeling of emptiness one of being conscious of the heart beat and dizziness The last may be associated with vertigo and pallor particularly if longer series of such ectopic beats occur Cerebral anaemia was considered the underlying mechanism by Wenckebach (1898) Regarding this last group of symptoms it is often impossible to be certain whether they are due to the arrhythmia or to an underlying anxiety state or neuro circulatory asthenia which are themselves so often responsible for or co exist with extra systoles (*see also* p 448)

Gallavardin (1914) reported an observation in a sixty three year old man with syphilitic aortic incompetence in whom auricular extrasystoles occurring periodically and then nearly always in the form of auricular bigeminy precipitated vertigo and syncope closely resembling Stokes Adams attacks

Opinions about how extrasystoles give rise to the various symptoms vary and much is still controversial The common varieties of palpitations described above are attributed to the same mechanism which is responsible for the accentuation of the first sound of the extrasystole (Ungerleider and Gubner) (*see* pp 463 *seq*) Others for instance Wenckebach and Winterberg hold the view that such sensations are produced by the first post-extrasystolic beat because of its larger stroke volume The observation that patients suffering from a concomitant cardiac condition resulting in an increased stroke volume (for example aortic incompetence) experience particularly unpleasant sensations from extrasystoles tends to support this view This conception does not however explain certain other symptoms commonly associated with this arrhythmia In cases with single isolated extrasystoles for example dizziness associated with a feeling of standstill of the heart might be attributed to the long post-extrasystolic interval It is true that in patients with advanced arteriosclerosis the diastolic blood pressure may fall to very low levels during a long post-extrasystolic interval and dizziness be produced in this way If it is remembered however that much longer intervals between successive ventricular beats as they occur in various kinds of heart block and in other conditions do not produce any symptom of this kind it becomes obvious that this cannot be the general explanation It seems probable that the extrasystole itself causes the sensation which is interpreted as standstill and gives rise to the feeling of unsteadiness This view is supported by Kline and Bidder s recent investigation on the origin of symptoms produced by extrasystoles which showed that they are caused by the premature contractions themselves Moreover in some patients with auricular fibrillation and extrasystoles only the latter produce unpleasant sensations which disappear if the ventricular ectopic beats are abolished while auricular fibrillation continues

An unusual symptom of some physiological interest is a short cough accompanying each extrasystole (Leconte) We encountered this phenomenon about ten times and in one further case a short cough invariably heralded the onset of an attack of auricular fibrillation lasting on an average six hours This kind of cough occurs without any warning and to the patient is both ominous and embarrassing as he realizes the invariable association with the cardiac arrhythmia and is taken by surprise by it It appears to be due to a reflex within the autonomous nervous system with the receptors in the heart itself

Discussion of symptoms may be concluded by a reference to notes left by a medical student apparently a non neurotic subject giving a vivid description of the suffering which extrasystoles can exceptionally cause (Weiss) The patient had subacute bacterial endocarditis and frequent extrasystoles These were a particularly distressing phenomenon much more so than one would glean from the textbooks and from the manner in which clinicians put aside the average patient s complaints as to skip beats The sensations were almost indescribable as if it were a cannon ball shot point blank at my brain Each extrasystole caused a terrific explosion occurring within the narrow and limited confine of a calcified skull This patient had also aortic incompetence the aggravating influence of which on the symptoms caused by extrasystoles was already referred to But even with a combination of these conditions suffering of such intensity fortunately is quite exceptional

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SIGNS ON PHYSICAL EXAMINATION

Inspection and Palpation

These two methods can with advantage be considered together Both were used a long time before the modern graphic registration of arrhythmias had become possible

Inspection refers to the jugular veins and to the praecordial area particularly the apex beat palpation to the latter and to the radial and carotid pulse

In an otherwise uncomplicated case with occasional single extrasystoles the individual premature beat gives rise in the jugular veins either to several smaller pulsations or to one larger wave depending on the time of occurrence of the extrasystole

If a premature beat falls at such a time that an auricular and a ventricular contraction occur simultaneously or nearly so the flow of blood in the normal direction from auricles to ventricles is temporarily obstructed and a large amount of blood ejected backwards into the jugular veins there giving rise to a much larger pulsation than those due to the normal beats Such conditions obtain if a premature ventricular systole occurs at about the time of the next auricular contraction or if an auricular extrasystole coincides with the preceding ventricular contraction—this is common in auricular extrasystoles—or in the case of atrio ventricular extrasystoles Failing such time relations between auricular and ventricular contraction the premature beat gives rise to two or three smaller pulsations the nature of each of which though analysable in graphic records cannot be determined by inspection

On inspection and palpation of the praecordial area the extrasystole produces a premature apex beat which often differs in character from that of the normal ones being sometimes weaker but more often more forceful and abrupt it is followed by a longer pause

In the radial and carotid pulse the extrasystole gives rise either to a premature smaller pulse its volume and timing depending on the degree of prematurity of the extra contraction which is followed by a longer pause or to no palpable pulse Many examples are contained in Mackenzie s book on the pulse (1902) In some instances a smaller pulse may be pal pable at the carotid but not at the radial arteries in others a pulse is absent in both

The absence of a palpable arterial pulse may be due either to the failure of the extra contraction to eject a sufficient amount of blood with a pressure adequate to open the aortic valves—this occurs most commonly in the case of very early extrasystoles—or to failure of the extrasystolic impulse to activate the ventricles which characterizes blocked auricular and certain rare varieties of atrio ventricular extrasystoles

If extrasystoles occur more frequently and particularly if one premature contraction follows each beat of the dominant rhythm the resulting bigeminal action has given rise to

controversy and great confusion in the past (*see* chapters on Alternans and on Coupling) If with bigeminal action the extrasystoles fail to produce a palpable pulse at the wrist the pulse rate is half the ventricular rate the resulting rhythm being one variety of pseudo bradycardia The first report of such an observation of what was then thought a double contraction of the heart in relation to the pulse seems to be contained in a paper by Charcelay published in *1838* The slow pulse is only too readily interpreted as indicating bradycardia and such misinterpretation is not infrequently carried a step further particularly in over digitalized patients with bigeminal action by diagnosing heart block In such instances inspection of the jugular pulse might well suggest the correct diagnosis which can then be substantiated by auscultation and if necessary established beyond doubt electrocardiographically (*see also* section on Diagnosis)

In interpolated extrasystoles the extracontraction gives rise to jugular pulsations and to an apex beat which are interspersed between two consecutive ones following one another in the regular sequence of the dominant rhythm no longer pause follows the last of such a group of three beats The arterial pulse changes are described in the section on interpolated extrasystoles Without auscultation neither palpation of the arterial pulse nor inspection of the jugular veins will make the diagnosis possible which often necessitates the employment of graphic methods

Auscultation

Just as apex beat and arterial and venous pulses so were the heart sounds produced by premature contractions studied long before the mechanism underlying the several varieties of intermittent pulse could be analysed according to modern standards The discrepancy between a stronger and more forceful apex beat an accentuated loud booming first sound and a weak pulse—which combination characterizes a large proportion of premature beats —was bound at an early stage to attract attention and promote speculation about the underlying mechanism Regarding observations in which in retrospect the underlying arrhythmia was most probably due to extrasystoles this phenomenon was first reported in 1870 by Quincke and already at that time attributed by him to lack of normal co ordination in the mode of contraction of such beats the effect of contraction of different parts of the heart partially cancelling one another perhaps under the influence of abnormal innervation

These conditions were studied especially in connexion with premature beats which did not give rise to a palpable pulse at the wrist or over the carotids Early investigators were Bozzolo (1876) one of the earliest correctly to attribute the small or absent pulse to inadequate filling of the ventricles and rejecting the then accepted theory of hemisystole (*see* chapter on Historical Remarks) Riegel and Lachmann who by experimental investigations and clinical observation gave this theory the *coup de grace* Stern (1884) Dehio (1891) Hochhaus and Quincke (1894) who termed such contractions frustran (abortive) and Hochhaus (1907) who stressed that the prematurity of such contractions is not the sole essential feature but that the qualitative difference as manifested in the different character of the apex beat and of the sounds were of fundamental importance Koranyi s paper may be quoted parenthetically as indicating that as late as 1908 a confusion could exist between time relations and relations of strength of such beats and that conclusions about their diagnostic significance functional effect and underlying mechanism could be put forward which nowadays can only be termed fantastic

The majority of extrasystoles produce two sounds but if the premature contraction fails to open the semilunar valves only the first sound is present In the case of bigeminal *rhythm this may easily be confused with gallop rhythm*

That the first sound of extrasystoles often is accentuated and of a quality different from that of the normal beats was noticed by many observers for example Quincke Hochhaus

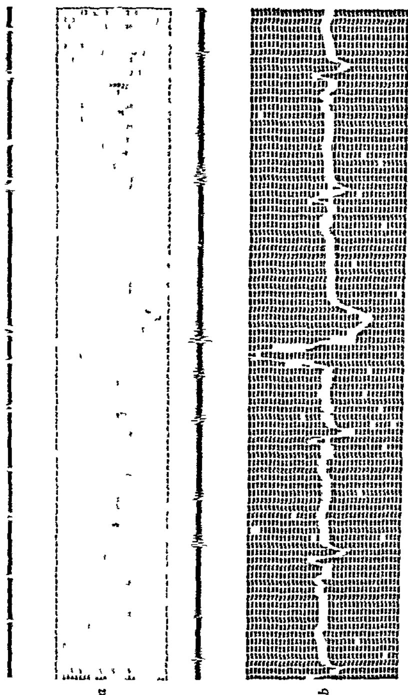


Fig. 01—*a* and *b*
For explanation see legend to Fig. 01—*c* on next page

and Quincke Hochhaus who stressed its boom ing character Wenckebach (1898 1903) who called it dumpf (dull) At first this accen tuation was explained by the qualitative differ ence in the mechanism of the extracontraction (Gerhardt Hochhaus 1907) and of the ejection of the blood (Leconte) It was also stated that the first sound of an extrasystole is particularly accentuated over that ventricle which is prim arily under strain to maintain compensation (Korányi Leconte) In other instances both sounds may be faint or even absent as was noted by Mackenzie

Some of these conditions are illustrated in the phonocardiograms reproduced in Fig 201

Phonographic investigations have shown that the first sound of extrasystoles may be louder or fainter than that of the normal beats and that the underlying mechanism is closely related to that responsible for the intensity of the first sound generally It is now accepted that this depends above all on the position of the A V valves at the beginning of ventricular contraction This view was first put forward as a provisional hypothesis by Wolferth and Mar golies (1930a) later confirmed and amplified by others (for example Dock who stressed the im portance of the degree of tension of the valves at the beginning of ventricular systole Cossio (for references see Cossio *et al* 1947) and recently re affirmed within limits by the original authors (1950) The position of the A V valves changes during auricular systole (Dean) and whatever the finer mechanism of this may be it is fairly certain that the eventual position of the valves at the moment of ventricular systole is the determining factor in the intensity of the sound produced (Levine and Harvey p 17) The A V valves are at first propelled downward into the ventricular cavities with auricular systole and then gradually proceed to a higher level Therefore if the ventricles contract very soon after the auricles (P R 0 04–0 12 second) the leaflets are quite low and relaxed and snap back a considerable extent This results in a loud sound If the ventricles contract at a time longer than normal after the auricles (P R 0 22–0 30 second) the valvular leaflets have already ascended to a higher position in the ventricles with the

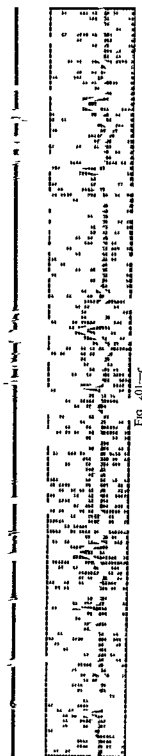


Fig 201 —Phonocardiograms of three instances of ventricular extrasystoles *a* and *b* on preceding page show that the extra systole had produced only one sound Fig 201—*c* shows two sounds produced by each extrasystole In all instances the first sound of the extrasystole was louder than that of the normal beats This is particularly pronounced in Fig 201—*c* which demonstrates in addition a systolic murmur in the first post extrasystolic beats which was not recorded with the other sinus beats

slack taken up and the first sound produced by the ventricular contraction in such circumstances is fainter (Levine and Harvey)

It was pointed out by Wolferth and Margolies (1930b) that both in auricular and ventricular extrasystoles the intensity of their first sound is dominated by the time relation between *the beginning of the P wave and the first sound of the premature beat* rather than by the degree of prematurity of the extrasystole This could be established by comparing the intensity of the first sound of extrasystoles with that of beats with a similar degree of prematurity in auricular fibrillation With the exception of very highly premature beats the first sound of extrasystoles tended to be louder than that of the normal ones if the interval beginning of P—first sound was less than that of the normal beats

Cossio Dambrosi and Warnford Thomson investigated the first sound in auricular and ventricular extrasystoles in some finer detail In all but one of sixteen cases with *auricular* extrasystoles the extrasystolic first sound was louder than that of the preceding and succeeding normal beats and compared with the normal beats the accentuated first extrasystolic sound occurred with a delay of an average of 0 03 second in relation to the QRS complex of the extrasystoles Both the increased intensity and the delay of the first sound of the extrasystoles were most pronounced if the premature beat occurred in mid diastole of the preceding beat Amongst fourteen cases with *ventricular* extrasystoles the extrasystolic first sound was louder than the normal first sound in nine of equal intensity in one of equal or less intensity in one and of less intensity in three cases in all instances it was delayed in relation to the onset of the QRS complex by an average of 0 05 second It was of greater intensity if the premature contraction occurred in mid diastole of the preceding beat or just after the next normal P wave The accentuation and delay of the first sound was more constant and more pronounced in auricular than in ventricular extrasystoles This was attributed by these authors to several factors auricular extrasystoles generally occur at a moment propitious for the accentuation of the first sound ventricular filling is more complete in auricular than in ventricular premature beats lastly in the former variety the normal synchronism in the closure of the tricuspid and mitral valves which by way of summation contributes much to the production of the first sound is undisturbed whereas in ventricular extrasystoles there is asynchronism in the contraction of the two ventricles The latter factor also accounts for the authors observation that in four of the fourteen cases of ventricular extrasystoles their first sound was split whereas that of the normal beats was not such splitting of the first extrasystolic sound was never observed in the case of auricular premature beats This accords well with the findings of Wolferth and Margolies (1935) that in cases of bundle branch block the split first sound has a right and a left ventricular component and that separation of these components is due to asynchronism in certain of the early phases of cardiac contraction in the two ventricles

It was stated above that in abortive extrasystoles only one sound is produced by the premature beat While this is nearly always the first sound Levine and Harvey published an instance in which only the second sound of a (ventricular) extrasystole was recorded (their Fig 105 on p 106) In the case of blocked auricular extrasystoles no sound may be heard or recorded

In nodal escape in which the normally synchronized contraction of the two ventricles follows the preceding auricular one at a short interval marked accentuation of the first sound may be noted (Levine and Harvey Fig 95 on p 98)

With interpolated extrasystoles the sounds of three beats occurring in quick succession are heard such group being followed by a normal interval

In patients with systolic murmurs and extrasystoles the murmur usually is fainter in the extrasystolic beat This was noted as early as 1884 by Stern (Case 2) also by Dehio (1891) and Hochhaus (1907) Weyler pointed out that diastolic murmurs cannot become manifest if the diastole is interrupted by an extrasystole in such instances the murmur occurs in

the diastolic phase of the extrasystole that is so late after the preceding beat that unless this sequence of events is borne in mind all sounds are erroneously attributed to the ectopic beat Systolic murmurs tend to be louder in the first post extrasystolic beat

The study of Wolferth and Margolies (1933) on gallop rhythm and the physiological third heart sound illustrates the value of the method of extrasystoles in the analysis of such acoustic phenomena These authors found that in all cases gallop as well as physiological third heart sounds fell without exception within one or both of two distinct time zones namely (1) 0 10–0 21 second after the beginning of the second heart sound that is protodiastolic or (2) 0 08–0 14 second after the beginning of the P wave that is presystolic When these two time zones become superimposed which may be due to a variety of causes (for example tachycardia) gallop rhythm may either appear for the first time or if already present become markedly accentuated this is due to a summation phenomenon The effect of extrasystoles on gallop rhythm was instructive In three cases with rapid heart rates loud gallop sounds and ventricular extrasystoles the loud gallop failed to appear during the compensatory post extrasystolic pauses but in each case during such pauses either protodiastolic or presystolic gallop sounds or both were present When the regular tachycardia was resumed the loud gallop sounds immediately recurred This separation of a loud summation gallop into less loud protodiastolic or presystolic sounds or both was attributed to the fact that the auricular contraction had become separated in time from the protodiastolic zone and thereby summation temporarily abolished Observations on two cases of auricular extrasystoles showed that when the premature beats occurred at a time so that they were superimposed on the protodiastolic period of the preceding beat a loud gallop sound invariably was recorded This demonstrates that even an aberrant auricular contraction timed in this way is capable of producing a summation phenomenon One similar observation was made in respect of the physiological third heart sound in a young varsity oarsman with auricular extrasystoles the third sound was heard and recorded only when the auricular systole of the premature beats fell in the range of ventricular protodiastole irrespective of whether or not the extrasystole was blocked Such observations were thus valuable for establishing that the gallop rhythm was in fact due to a summation phenomenon

SUMMARY

Inspection and Palpation

In an otherwise uncomplicated case occasional single extrasystoles give rise in the jugular veins either to two or three small pulsations or to one larger wave depending on the time of occurrence of the premature beat Such time relations are discussed

The apex beat produced by a single extrasystole is not only premature and followed by a longer pause but also often differs in character from that of the normal beats

In the radial and carotid pulse an extrasystole either gives rise to a premature smaller pulse followed by a longer pause or fails to produce a palpable pulse The mechanism underlying the latter phenomenon is briefly discussed In the event of bigeminal heart action due to one extrasystole following each beat of the dominant rhythm absence of an extrasystolic palpable pulse results in the pulse rate being half the ventricular rate in such cases the pulse often is slow and this may be misinterpreted as being due to bradycardia or complete heart block

Auscultation

The majority of extrasystoles produce two heart sounds but if the premature contraction fails to open the semilunar valves only the first sound is present If this occurs in association with bigeminal heart action such sequence of three sounds may be misinterpreted as gallop rhythm

slack taken up and the first sound produced by the ventricular contraction in such circumstances is fainter (Levine and Harvey)

It was pointed out by Wolferth and Margolies (1930b) that, both in auricular and ventricular extrasystoles the intensity of their first sound is dominated by the time relation between the beginning of the P wave and the first sound of the premature beat rather than by the degree of prematurity of the extrasystole This could be established by comparing the intensity of the first sound of extrasystoles with that of beats with a similar degree of prematurity in auricular fibrillation With the exception of very highly premature beats the first sound of extrasystoles tended to be louder than that of the normal ones if the interval beginning of P—first sound was less than that of the normal beats

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CLINICAL DIFFERENTIAL DIAGNOSIS

Single Extrasystoles

On routine clinical examination an extrasystole is characterized by the signs of a premature contraction which is followed by a longer interval The presence of such a premature beat can without difficulty be ascertained by inspection palpation and particularly by auscultation so that the diagnosis can easily be made And extrasystoles are so much the commonest cause of this kind of disturbance of rhythm that in the great majority of instances the clinical diagnosis will be correct

But this is not always the case In various chapters of this book conditions are described which can easily be mistaken for extrasystoles whereas their nature and clinical significance actually are entirely different Conversely extrasystoles may be missed or the extrasystolic arrhythmia erroneously be attributed to some other mechanism

A few examples dissociation with interference invariably conveys the clinical impression of an arrhythmia due to extrasystoles in this instance the differential diagnosis can only be made by graphic methods The same holds good for that between extrasystoles in the strict sense of the term as employed in this book and parasystole though in the latter the varying coupling may arouse the suspicion of a more complicated arrhythmia Dropped beats after a varying number of conducted ones can *to a certain extent* be distinguished from extrasystoles by the absence of any sound indicating a premature beat but without graphic methods a differential diagnosis between occasional dropped beats and blocked auricular extrasystoles cannot be made with any degree of certainty only the differences in the venous pulse may suggest the underlying condition Occasional extrasystoles during auricular fibrillation also require graphic methods for their recognition

In cases in which a variable number of extrasystoles follow a variable number of sinus beats the differentiation from auricular fibrillation may be extremely difficult Moderate exercise for example raising the body from the supine position a few times or inhalation of amyl nitrite tend to increase the irregularity of rhythm in auricular fibrillation whereas extrasystoles are likely to be suppressed by such measures and the rhythm thus tends temporarily to become regular in this way a differential diagnosis is sometimes possible

Attempts have repeatedly been made—in our opinion without success—at distinguishing by clinical examination alone between auricular and ventricular extrasystoles The only condition in which we believe this to be possible is mitral stenosis if a distinct presystolic murmur not associated with a diastolic one is present over the apical region If such murmur which is due to auricular contraction can distinctly be heard to precede the first sound of the extrasystole its auricular origin can be assumed In the presence of a diastolic murmur this method is unreliable since a diastolic murmur occurring immediately before an extrasystole may simulate a presystolic one (Mond) Mond claimed that the differentiation between auricular and ventricular extrasystoles was possible by ascertaining whether the first alteration produced in the venous pulse by the extrasystole occurred before or after the first sound the former indicating an auricular the latter a ventricular origin of the premature beat We are not convinced that this method is either practicable—in many cases the several pulsations of the venous pulse cannot be distinctly seen—or reliable

It has also been claimed that the distinction between these two types of extrasystoles could be made by tapping out the timing of the underlying rhythm since this was shifted by an auricular but not by a ventricular premature beat This method is bound to be quite unreliable in view of the great number of unpredictable factors which determine the length of the post-extrasystolic interval after an auricular extrasystole (*see* section on Auricular Extrasystoles) A simple sinus arrhythmia too makes such an attempt fail (Katz)

The first sound of extrasystoles may be louder or fainter than that of the normal beats of the individual case The importance of the position of the A V valves at the beginning of ventricular systole in determining the intensity of the first heart sound is emphasized This in the case of premature beats is thus intimately related to the interval beginning of the auricular contraction—first sound of the extrasystole

In blocked auricular extrasystoles no sound may be present

In nodal escape the first sound tends to be particularly loud

In auricular as well as ventricular premature beats the first extrasystolic sound is delayed in relation to the QRS complex of the extrasystole as compared with the time relations in normal beats In ventricular but not in auricular premature beats the first sound is occasionally split the underlying mechanism of this phenomenon is discussed

In patients with a systolic murmur and extrasystoles the murmur tends to be fainter in the premature beats Diastolic murmurs may be delayed by an extrasystole becoming audible in the diastolic period of the extrasystole

Observations on patients with gallop rhythm and extrasystoles supported the view that one form of gallop rhythm is a summation phenomenon due to superimposition of acoustic phenomena occurring in two distinct portions of the cardiac cycle namely a protodiastolic and a presystolic time zone

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which governs in the first place the physician s attitude and action To the lay person irregular heart action spells heart disease and nowadays more people than ever are heart conscious Nearly every one has had relatives or friends die of heart disease often suddenly and much publicity is given to this topic in the press and popular books with the inevitable result that any irregularity in the customary rhythm of his pulse or heart beat makes the patient apprehensive of the dreaded disease

In the treatment of this group of patients the two most important conditions for success are to take the patient s complaint seriously and to carry out a complete and thorough examination including the taking of a detailed history

The patient s complaints must be taken seriously if only because his physical symptoms and even more his anxiety are very real To tell a patient after a cursory examination your heart is perfectly sound and those few missed beats don t mean a thing results only in the patient s seeking medical advice elsewhere there are not many conditions in which patients change doctors as often as with extrasystoles

A complete and thorough examination is indispensable not only in order to exclude the presence of any other pathological condition cardiac or otherwise which may and often does require treatment but also for psychological reasons If a patient is to be reassured that he is otherwise healthy which in this group of patients is the crucial and decisive therapeutic measure such assurance must be given in an authoritative decisive manner making impossible any doubt in the patient s mind about its accuracy and good faith and it can carry such weight only if the patient is convinced that all possible steps were taken to exclude any other disease

In taking a detailed history special attention should be paid to the patient s mode of life and habits In quite a number of cases extrasystoles can be abolished if the patient gives up excess of coffee or tea particularly if these beverages are taken strong or if he reduces smoking or changes his dietetic habits Regarding the last the avoidance of flatulence *of indigestible articles of food or copious meals are points of special importance* In others adequate treatment of constipation may cure the extrasystoles An enquiry into the taking of drugs should not be omitted extrasystoles may be the result of the taking of thyroid for slimming or of ephedrine or epinephrine (for example for asthma) Regarding digitalis *see* below under (3)

In some cases one has to go into great detail regarding the patient s habits Thus an elderly patient who has been well known to one of us for many years used to have numerous ventricular extrasystoles as a young man without any evidence of any other cardiac abnormality The extrasystoles disappeared under appropriate treatment and were in abeyance for many years until one day he again sought advice in great anxiety because all my old trouble has come back He was greatly troubled by numerous extrasystoles most of the early afternoon and closer questioning elicited the statement that at the time the trouble recurred he had adopted the habit of taking a cup of tea at about 3 p m Discontinuing this newly acquired habit resulted in the prompt disappearance of the symptoms and it was noteworthy that in his case tea precipitated extrasystoles only when taken in the early afternoon whereas he could take a much greater quantity for breakfast without any ill effects

Extrasystoles occurring during the menopause can often be successfully treated by means of ovarian hormone preparations if other measures including sedatives have failed In patients in whom premature beats appear during pregnancy assurance about their frequent occurrence and their innocuous character is nearly always all that is required

In the majority of cases of this group however no such precipitating factor can be found and it is then necessary to explain to the patient the harmlessness of his condition simple terms and a convincing manner The way in which such explanation is given depe of course on the patient s personality In many cases it will be sufficient to stress the

infrequently the first or the presenting sign in patients with coronary sclerosis in well as in those with chronic mitral valvular disease they often herald the onset of fibrillation or flutter This holds good particularly for auricular extrasystoles wit shape of P waves

As far as the small number of reported cases makes possible to judge the p significance parasystole and return extrasystoles seem to occur predominantly in with structural heart disease Dissociation with interference appears on the wh to be associated with other cardiac abnormalities toxic or structural in nature

In practice and considering extrasystoles and ectopic arrhythmias generally hardly do better than apply to all age groups the precept which Ritchie gave in r patients over forty with extrasystoles namely to regard the presence of any ectopic mia with suspicion in every case and to examine the patient with every care At tim examination will reveal—perhaps a hitherto unsuspected—cardiac disease or sor systemic disorder for example chronic gall bladder disease and the prognosis will determined by that of the underlying condition but in the great majority of insta extrasystoles will be found to be of the harmless variety and to have no prognostic cance

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TREATMENT

β λ α ν δε α α ε το
προσω α ω το α π τηδειου απεχ ν

The best advice is that which is least unsuitable
Hippokrates *Tradition in Medicine*
Trans by Chadwick and Mann

The great majority of patients with extrasystoles do not require treatment The pa is not aware of the arrhythmia which in very many cases is harmless and often discov accidentally during a medical examination

There are three main conditions in which extrasystoles necessitate treatment

1 If in the absence of any other pathological condition they give rise to symptoms clinical importance physical or psychological

2 If they are very numerous

3 If they occur in association with other pathological conditions in which they may initiate auricular or ventricular fibrillation or may further impair cardiac function

1 Treatment of extrasystoles because of clinical symptoms, in the absence of any other pathological condition

While the great variety of symptoms which can be produced by extrasystoles is discussed in the appropriate section it is the psychological effect of the irregular heart action which usually is the predominant cause to make the patient seek medical advice and it is this aspect

which governs in the first place the physician s attitude and action To the lay person irregular heart action spells heart disease and nowadays more people than ever are heart conscious Nearly every one has had relatives or friends die of heart disease often suddenly and much publicity is given to this topic in the press and popular books with the inevitable result that any irregularity in the customary rhythm of his pulse or heart beat makes the patient apprehensive of the dreaded disease

In the treatment of this group of patients the two most important conditions for success are to take the patient s complaint seriously and to carry out a complete and thorough examination including the taking of a detailed history

The patient s complaints must be taken seriously if only because his physical symptoms and even more his anxiety are very real To tell a patient after a cursory examination your heart is perfectly sound and those few missed beats don t mean a thing results only in the patient s seeking medical advice elsewhere there are not many conditions in which patients change doctors as often as with extrasystoles

A complete and thorough examination is indispensable not only in order to exclude the presence of any other pathological condition cardiac or otherwise which may and often does require treatment but also for psychological reasons If a patient is to be reassured that he is otherwise healthy which in this group of patients is the crucial and decisive therapeutic measure such assurance must be given in an authoritative decisive manner making impossible any doubt in the patient s mind about its accuracy and good faith and it can carry such weight only if the patient is convinced that all possible steps were taken to exclude any other disease

In taking a detailed history special attention should be paid to the patient s mode of life and habits In quite a number of cases extrasystoles can be abolished if the patient gives up excess of coffee or tea particularly if these beverages are taken strong or if he reduces smoking or changes his dietetic habits Regarding the last the avoidance of flatu lence of indigestible articles of food or copious meals are points of special importance In others adequate treatment of constipation may cure the extrasystoles An enquiry into the taking of drugs should not be omitted extrasystoles may be the result of the taking of thyroid for slimming or of ephedrine or epinephrine (for example for asthma) Regarding digitalis *see* below under (3)

In some cases one has to go into great detail regarding the patient s habits Thus an elderly patient who has been well known to one of us for many years used to have numerous ventricular extrasystoles as a young man without any evidence of any other cardiac ab normality The extrasystoles disappeared under appropriate treatment and were in abeyance for many years until one day he again sought advice in great anxiety because all my old trouble has come back He was greatly troubled by numerous extrasystoles most of the early afternoon and closer questioning elicited the statement that at the time the trouble recurred he had adopted the habit of taking a cup of tea at about 3 p m Discontinuing this newly acquired habit resulted in the prompt disappearance of the symptoms and it was noteworthy that in his case tea precipitated extrasystoles only when taken in the early afternoon whereas he could take a much greater quantity for breakfast without any ill effects

Extrasystoles occurring during the menopause can often be successfully treated by means of ovarian hormone preparations if other measures including sedatives have failed In patients in whom premature beats appear during pregnancy assurance about their frequent occurrence and their innocuous character is nearly always all that is required

In the majority of cases of this group however no such precipitating factor can be found and it is then necessary to explain to the patient the harmlessness of his condition in simple terms and a convincing manner The way in which such explanation is given depends of course on the patient s personality In many cases it will be sufficient to stress the great

frequency of this arrhythmia in healthy people in others a short talk on the normal mechanism of the heart beat and the harmlessness of an occasional beat arising elsewhere in the heart and momentarily interfering functionally with the rhythm will be helpful Some patients appreciate a simple explanation of the post extrasystolic pause as this allays the anxiety which many patients have because the heart stood still for such a long time

In most instances of this group it is advisable to await the effect of such explanatory talks before resorting to drugs Sometimes the successful treatment of the anxiety caused by the arrhythmia results in the disappearance or rarer occurrence of the extrasystoles But even if this is not the case once the patient is reassured about the innocuous character of the irregularity he soon learns to disregard the missed beats and no further treatment may then be necessary A certain proportion remain however in which symptoms continue to be so troublesome that an attempt should be made to abolish the extrasystoles by pharmacological means In such cases quinidine is the drug of choice and its successful early use preferably for a short time is also of great psychological importance since it demonstrates to the patient that means are available to rid him of his troubles Details of quinidine treatment are given below

2 Treatment of Extrasystoles because of their great numbers, in the absence of any other Pathological Condition

In this group drug treatment of the condition is usually necessary not only because *symptoms are more pronounced but also because very numerous extrasystoles may have* the same effect on the general circulation as more pronounced tachycardia, namely reduced cardiac output with all its consequences Such great numbers are however more frequently found in association with other pathological conditions as discussed immediately below

3 *Treatment of Extrasystoles occurring in association with* certain other Pathological Conditions

In a certain proportion of cases of this group the arrhythmia is found to be precipitated by or at least associated with some *extracardiac* pathological condition for example chronic gall bladder disease hyperthyroidism anxiety state etc In such instances treatment of the underlying condition obviously is the appropriate approach

Regarding the treatment of extrasystoles in *cardiac* patients two main considerations determine the indication of treatment of extrasystoles

(*a*) An associated pathological condition in which extrasystoles are known often to be precursors of fibrillation namely auricular extrasystoles of auricular ventricular extrasystoles of ventricular fibrillation and

(*b*) Structural myocardial disease in which apart from (*a*) the additional impairment of cardiac function produced by the arrhythmia calls for its treatment

Conditions in which *auricular* extrasystoles are known frequently to be precursors of auricular fibrillation are mitral valvular lesions and coronary disease In these two conditions treatment of the arrhythmia is indicated if only to postpone the onset of auricular fibrillation Auricular extrasystoles occurring in myocardial infarction call for prompt *treatment for the same reason they may be associated with other auricular arrhythmias* and to a certain extent may indicate possible auricular infarction (see section on Coronary Disease) Multiform *ventricular* extrasystoles occurring in coronary or myocardial disease always call for immediate treatment as they are an unequivocal danger signal of threatening ventricular fibrillation This is particularly important if they occur after an attack of myocardial infarction More numerous ventricular extrasystoles arising from the same

focus occurring in coronary or myocardial disease or after myocardial infarction have to be treated for the same reason moreover in such conditions the extrasystolic arrhythmia further impairs the already reduced cardiac efficiency and for this reason too every effort has to be made to regularize the cardiac rhythm by drug treatment Regarding extra systoles due to digitalis see p 283

The two most important drugs for the treatment of extrasystoles are quinidine sulphate and digitalis Certain other compounds are also recommended and in some cases admit tedly effective they will be briefly discussed at the end of this section Of these procaine amide which has recently been introduced may well acquire special importance

Quinidine

Regarding the mode of action of this drug and a discussion of experimental and clinical observations see section on Quinine and Quinidine

In connexion with the clinical employment of quinidine which in the vast majority of cases is given by mouth as quinidine sulphate two points should be emphasized some individuals are hypersensitive to it and the drug is quickly eliminated

Owing to the former it has become a generally accepted practice except in emergencies to give at first one test dose of 0 2 gramme of quinidine sulphate If no toxic symptoms occur (*see* below) systematic treatment is started the following day The individual dose as well as the spacing of the doses has to be adjusted according to the patient s individual reaction and requirement which vary widely As initial doses we recommend

0 2 gramme thrice daily in the treatment of troublesome extrasystoles in otherwise healthy individuals

0 2 gramme four hourly in the treatment of extrasystoles of the above groups (2) and (3)

The effect of the drug can usually be assessed within twenty four hours The subsequent optimum dose is the smallest effective individual dose given at the longest intervals without the persistance or re appearance of the arrhythmia Thus if with initial doses given as indicated above extrasystoles occur before the next dose is given the drug should be ad ministered at shorter intervals if the individual dose of 0 2 gramme is inadequate to suppress the ectopic beats larger doses for example 0 4 and in some rare cases even 0 6 gramme have to be given

Once cardiac rhythm has become regular it is advisable to continue the exhibition of quinidine for about one week in the same minimum dosage and at the same maximum intervals which have proved effective Subsequently the number of daily doses is gradually reduced and if the individual single dose exceeded 0 2 gramme this also is gradually decreased It is common experience that with this method extrasystoles remain in abey ance even if the drug is finally discontinued This is however not always the case Should they recur in an otherwise healthy subject it is often not necessary to re institute the drug since the patient has learned to disregard the occasional missed beats But if the arrhyth mia recurs in cardiac patients associated with conditions listed above under (3) prolonged exhibition of quinidine is indicated provided that no toxic symptoms occur

The commonest of these—cinchonism—are nausea vomiting and diarrhoea tinnitus deafness and urticaria A host of others have been observed but they are less common for example abdominal pain (Jamieson) headache and dizziness marked rise in tem perature (Sturnick) blurring or mistiness of vision (Clark Kennedy) photophobia diplopia scotomata even temporary blindness (Jezer and Schwartz) and optic atrophy Pruritus (Wolff and White) and exanthemata (papular or scarlatiniform Clark Kennedy) have been observed also sweating fullness in the head flushes excitement confusion and rarely syncope Gordon *et al* reported apnoea and respiratory paralysis with collapse

and Licciardello and Stanbury observed acute haemolytic anaemia Occasionally the drug produces intraventricular block (White Marvin and Burwell) or ventricular tachycardia (two such instances were reported by Wolff and White) Any of these signs of cinchonism calls for discontinuing the drug Whether after the subsidence of toxic symptoms the drug should be re instituted must be judged individually and much must be left to the physician s experience and judgement

Quinidine is certainly the most efficacious drug for the suppression of extrasystoles though not effective in every case (Deschamps Lian and Blondel) Smith (1922) found a marked reduction in the number of extrasystoles in seventeen out of twenty patients that is in 85 per cent and Barrier reported a similar proportion (90 per cent) of successes in his cases Our personal experience is in agreement with this figure

In one instance of ventricular tachycardia following myocardial infarction Levine and Stevens found it necessary to give 1 5 grammes of quinidine five times daily in order to abolish the arrhythmia This report is quoted as an instance of an exceptionally large dose In cases of this kind procaine amide may well take the place of such excessive doses of quinidine

The intravenous administration of quinine introduced in the treatment of extrasystoles by Hecht and Zweig (1917) and later advocated by Singer and Winterberg (1922) is rarely necessary and the same holds good for the intravenous use of quinidine sulphate (0 2–0 4 gramme in 10 0 cc to be given very slowly or as a drip infusion) This method is not free from risk sudden collapse may occur particularly in patients with myocardial disease if the injection is given too quickly and even small doses of quinine or quinidine given intravenously to patients with heart block have caused ventricular fibrillation (Schwartz and Jezer Smith *et al* 1940 Sagall *et al*) Collins recommended the intravenous administration of quinidine lactate in doses of 0 2–0 4 gramme for the treatment of acute arrhythmias including extrasystoles during clinical anaesthesia The nature of the arrhythmias was however diagnosed entirely on clinical grounds

It cannot be denied that in certain emergencies for example numerous or multiform extrasystoles and ventricular tachycardia complicating myocardial infarction or occurring as a result of digitalis intoxication the intravenous injection of quinidine may be life saving In such contingencies the risk inherent in the patient s condition outweighs that taken by the intravenous administration of the drug Further investigations about the efficacy of pro caine amide in such conditions have to be awaited before the relative merits of this new drug and that of the intravenous administration of quinidine in such emergencies can be assessed

The intramuscular route more recently employed for soluble quinidine and for quinine (quinine dihydrochloride 0 5 gramme) is certainly less risky than the intravenous one but in most cases of extrasystoles equally unnecessary

Digitalis

In normal subjects digitalis preparations abolish extrasystoles in a large proportion of cases Multiform extrasystoles too if they are not precipitated by digitalis are suppressed by this drug and are no contra indication against its employment It takes however second place to quinidine for various reasons The action of quinidine on the heart is less complex and more specific regarding the suppression of ectopic beats and the drug is far more quickly eliminated without cumulating Another reason is psychological the use of digitalis in the treatment of heart disease is well known to lay persons nowadays and its employ ment solely for the abolition of extrasystoles is bound to be misinterpreted by the patient as signifying the presence of the dreaded disease however well reasoned the physician s ex planation may have been the result of the prescription will be that the patient comes to doubt the assurance and to distrust the physician

The two conditions in which we recommend to use digitalis for the suppression of extrasystoles are

(1) failure of quinidine to achieve the desired result and

(2) an associated cardiovascular condition in which digitalis is indicated for example congestive heart failure

Regarding (2) it should be stressed that the presence of extrasystoles in congestive heart failure not only is no contra indication against its use but an additional indication Not infrequently some confusion regarding the exhibition of digitalis is seen to arise between the significance of extrasystoles existing *before* the commencement of digitalis therapy and those occurring *during* such treatment While the former are by no means a contra indication the latter call for great caution in the further exhibition of the drug in most cases necessitating reduced doses and often discontinuing the drug at least temporarily (see section on Digitalis)

In some instances great discrimination in deciding whether or in what dosage digitalis should be continued is required Thus in a woman of forty seven with Lutembacher s syndrome at first sinus rhythm with occasional ventricular extrasystoles was present sub sequently auricular flutter developed with occasional extrasystoles Soon after digitalis treatment had been started with the object of converting flutter into fibrillation coupled beats were recorded due to one ventricular extrasystole following each conducted beat Contrary to the generally accepted rule it was decided in that case to continue with digitalis though temporarily to reduce the dose since extrasystoles were known to have occurred prior to the exhibition of the drug the extrasystoles in the electrocardiogram all had the same shape and as far as ascertainable in a short record their coupling to the preceding beat was constant These features seemed to lessen the risk of precipitating ventricular tachycardia The further development showed this assumption to have been correct with further judicious use of digitalis the number of extrasystoles decreased and conversion into auricular fibrillation was achieved on the eighth day of digitalis treatment (Schott) It should be emphasized that such cases are rare exceptions In most cases the occurrence during digitalis treatment of extrasystoles in any but the smallest numbers calls for tem porarily discontinuing the drug

The employment of digitalis in very small doses for the treatment of extrasystoles was recommended by Wenckebach in 1910 In undigitalized and otherwise normal patients the usual daily dose is 0 05–0 1 gramme of powdered leaves given in divided doses (see also Wenckebach and Winterberg) This method was widely used before the advent of quinine and quinidine Instead of the powdered leaves one of the purified glucosides can with advantage be given our personal preference being for Digoxin obtained from *digitalis lanata* in doses of 0 25 mg three times a day initially once or twice a day subsequently If digitalis is given to patients with congestive heart failure and extrasystoles the dose depends on the underlying condition Whatever preparation is given the patient must be kept under supervision because of the possible occurrence of signs of digitalis intoxication The most important ones are anorexia nausea and vomiting and the re appearance of extrasystoles after they had been abolished also ectopic ventricular tachycardia If digitalis is taken for longer periods yellow vision and drowsiness (resembling pre uraemia) may be the first signs of drug intoxication

The efficacy of digitalis in suppressing extrasystoles auricular as well as ventricular in origin has repeatedly been confirmed (Christian Otto and Gold Schwartz)

In the past particularly in Central Europe a combination of digitalis quinine (or quinidine) and strychnine was popular It was known as Wenckebach s pills which contained quinidine sulphate 0 04 gramme digitalis (powdered leaves) 0 02 gramme

strychnine nitrat 0 0006 gramme The usual dose was 3–6 pills daily The efficacy of strychnine for this purpose seems questionable (see section on Strychnine)

Other Drugs

The drugs briefly discussed below have all occasionally been used successfully in the treatment of extrasystoles but with the possible exception of the recently introduced procaine amide their effect is far less constant and they have to be considered as much inferior to quinidine and digitalis The pharmacological action of these drugs in relation to ectopic beats is discussed in the appropriate sections in the chapter on drugs where it was shown that a great variety of compounds may cause as well as abolish extrasystoles In the following paragraphs some supplementary remarks will be found on their clinical application

Procaine Amide (Pronestyl)

This drug has been introduced in the treatment of extrasystoles and ventricular tachycardia so recently that further investigations have to be awaited before its value can be assessed The reports so far available indicate that it is promising The effective oral dose was found to vary widely in different patients In patients with ventricular extrasystoles doses varying between 0 4 and 1 0 gramme given either orally or intravenously proved effective to suppress the arrhythmia for a period varying from a few minutes to many hours In some cases the drug had to be given for longer periods and the suggested maintenance doses range from 0 5 to 1 0 gramme every three to six hours This drug proved particularly effective in abolishing ventricular tachycardia (usual initial dose 1 25 grammes followed in one hour by an additional 0 75 gramme if the tachycardia persisted) The chief side effects were hypotension with the intravenous route and nausea and vomiting with oral administration If administered intravenously the drug must be given very slowly (100 mgm per minute or less) and with constant control of blood pressure and electrocardiogram For some further details and references see section on Cocaine p 309

Novocaine (Procaine)

In doses of 100 mgm given intravenously procaine has been successfully used in the treatment of extrasystoles occurring suddenly and especially in that variety occurring during anaesthesia It has also been employed in extrasystolic arrhythmias occurring after myocardial infarction It seems fairly certain that procaine amide will supersede novocaine (procaine) in the treatment of such arrhythmias

Potassium Salts

Potassium acetate given as a 25 per cent solution in peppermint water in doses of two to four grammes every four to six hours has been recommended repeatedly, especially for the treatment of extrasystoles due to digitalis intoxication This method should be considered particularly in patients in whom quinidine or Pronestyl cannot be given because of intolerance to these drugs especially in instances of digitalis extrasystoles Impaired renal function is an important contra indication

Physostigmine

was recommended by Hecht and Zweig in daily doses of 3 mgm and is sometimes replaced by Prostigmine

Atropine and Belladonna Preparations

were sometimes used and Laubry recommended them as late as 1953 It seems certain that such drugs may occasionally abolish extrasystoles but the side effects are by no means negligible

Papaverine

Although this drug has been claimed to suppress extrasystoles for the reasons discussed in the section on this drug (p 335) we do not recommend its use for the sole purpose of treating extrasystoles

Fagarine

which can only be given intramuscularly cannot be recommended because of dangerous side effects

Epinephrine and Ephedrine

were occasionally employed their use should be discouraged since more often than not they cause rather than abolish ectopic beats

SUMMARY

The great majority of patients with extrasystoles do not require treatment Three main conditions are listed in which extrasystoles necessitate treatment

(1) If in the absence of any other pathological condition they give rise to symptoms of clinical importance physical or psychological
(2) If they are very numerous
(3) If they occur in association with other pathological conditions in which they may initiate auricular or ventricular fibrillation or may further impair cardiac function

Regarding the above group (1) the importance of taking the patient s complaints seriously and of carrying out a complete examination is emphasized Attention in great detail must be paid to the patient s mode of life some re adjustment of which often ensures successful treatment of the arrhythmia In many cases no precipitating factor can be found treatment of such cases necessitates appropriate explanation and re assurance about the innocuous character of the arrhythmia The importance of the right psychological approach is stressed In this group of cases drug treatment becomes necessary only if symptoms continue to be so troublesome that they interfere with a normal mode of life

In the above group (2) drug treatment of the premature beats is usually necessary because of the severity of symptoms and of the frequent impairment of circulatory efficiency caused by the pronounced arrhythmia

Regarding the above group (3) in some cases the extrasystolic arrhythmia is found to be associated with or precipitated by an extracardiac condition in such instances treatment of the underlying condition is the first line of approach

In cardiac patients with premature beats the necessity of treating *auricular* extrasystoles in patients with mitral valvular lesions and coronary disease and multiform or numerous uniform *ventricular* extrasystoles in patients with coronary or myocardial disease is stressed The two most important drugs for the treatment of extrasystoles are quinidine and digitalis The mode of employment of these drugs including dosage and signs of drug intoxication is discussed in some detail Amongst other drugs recommended for the treatment of

extrasystoles procaine amide seems promising particularly in the treatment of ventricular extrasystoles and ventricular tachycardia but the result of further investigations has to be awaited before its value can be assessed This holds good particularly in regard to the relative merits of procaine amide and the intravenous use of quinidine in emergencies Other drugs briefly discussed are novocaine potassium salts physostigmine atropine and belladonna preparations papaverine fagarine and epinephrine and ephedrine Of these potassium salts seem to deserve consideration novocaine has been superseded by the recently introduced procaine amide The remaining ones cannot be recommended and the use of fagarine epinephrine and ephedrine in the treatment of extrasystoles should definitely be discouraged

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CHAPTER XII

THE MECHANISM UNDERLYING THE ORIGIN OF EXTRASYSTOLES AND OF ECTOPIC AUTOMATIC BEATS

INTRODUCTORY REMARKS

The discussion in the various chapters of this book will have made it apparent that the mechanism underlying the different forms of ectopic arrhythmias varies Thus in dissociation with interference beats giving the impression of being extrasystoles were shown actually to be sino auricular ones interfering at times with an otherwise regular A V rhythm Return extrasystoles can be assumed to be due to two successive activations of the ventricles by the same impulse In parasystole the co existence of two centres exhibiting automatic impulse formation can be considered established Other instances of arrhythmias simulating the presence of extrasystoles were mentioned in the chapter on Coupling

None of the above mechanisms is in our opinion responsible for those ectopic beats which are *extrasystoles* in the strict sense of the term as used in this book namely *ectopic beats with accurate coupling to the preceding beat* In the present chapter their mode of origin will be discussed and their relationship to automatic beats considered In doing so we hope to substantiate our contention that this variety of ectopic arrhythmias should be separated from the others

It seems to us that a discussion of this subject touches upon several aspects of great physiological importance while in view of the common clinical occurrence of extrasystoles it should not be without some clinical interest

It has to be admitted at the start that our knowledge about this problem is very scanty As long as the mechanism of the normal cardiac impulse formation is incompletely understood our knowledge about that of the more complicated ectopic ones is of necessity very imperfect—to say the least We believe however that recent advances in physiology make it possible to obtain a somewhat clearer picture of the underlying processes than had previously been the case

Our thesis is that true extrasystoles are precipitated in the ectopic centre by the preceding beat and are thus a passive derivative phenomenon as distinct from those forms of ectopic arrhythmias (for instance parasystole) in which two independent automatic centres of equal importance of impulse formation co exist the activity of neither of which is deriving from that of the other

Our thesis stated in this form is from one point of view the reverse of what was held by some of the most competent authorities not so long ago we refer to the conception that true extrasystoles were to be classified amongst the active heterotopic rhythms as distinct from passive ones amongst which were escaped beats and similar abnormal rhythms such as A V or idio ventricular rhythms called escape rhythms (Ersatzrhythmen Wenckebach and Winterberg 1927) this latter group was thought to occur passively as the result of failure of normal beats to be initiated or to be conducted This is one aspect of the conception then held already for some time by several authorities that there was a fundamental difference in the mechanism of origin and in the nature of such beats true extrasystoles were considered to be due to a kind of stimulus different from the physiological one and distinguished as heterogenetic from the normal homogenetic ones (Lewis 1911) or heterotypic

as distinct from nomotypic (Hering 1911) But Lewis himself under the influence of Kaufmann and Rothberger s work on parasystole became doubtful about this distinction and in the third edition of his book (1925) stated that he was unable to rewrite with sufficient confidence those distinctions between homogenetic and heterogenetic impulses which I emphasized in the last edition of this book That such a distinction though in a different way of application is in fact justified in our opinion will be shown in this chapter

The idea that extrasystoles with accurate coupling are precipitated by the preceding beat is of course an old one But much controversy has existed regarding the strict separation of this group and its relationship with others Some of these views will first be discussed

ALTERNATIVE HYPOTHESES

Extrasystoles and Parasystole

At one time attempts were made to explain *all* ectopic arrhythmias on the basis of a parasystolic mechanism and extrasystoles with accurate coupling were thus also considered to be due to the independent activity of an ectopic centre that is to be automatic in origin In the chapter on pararrhythmias reasons were given why this view is untenable The main arguments may here be summarized by recalling that two of the three main features of parasystole are absent in the common variety of extrasystoles namely varying coupling of the ectopic beats and the occurrence of combination (= fusion) beats The further hypothesis that the accurate coupling of the extrasystoles is due to a tendency of the normal and of the—presumed automatic—ectopic rhythms to occur in simple mathematical relations to one another (Kaufmann and Rothberger 1922) was an obvious *petitio principii* and this relationship could be shown to be the *result* and not the *cause* of the accurate coupling of the extrasystoles

With rare exceptions (for example Schaefer 1951) the view that extrasystoles are due to a parasystolic mechanism has now generally been abandoned and it is significant that Rothberger its most important protagonist at one time finally gave it up himself (Rothberger 1932)

Circus Movement and Re-entry Mechanism

The theory of circus movement widely accepted until recently as an explanation of the mechanism of auricular fibrillation and flutter though seriously called in question of late has also been applied to account for that of extrasystoles Mines (1913) seems to have been the first to have considered this possibility

The essence of circus movement and its experimental basis are described in the sections on return extrasystoles and on flutter and fibrillation (*q v*) Suffice it to say here that in this condition a wave of excitation is assumed to circulate in certain pathways of the excitable tissue the same impulse thus activating successive portions of the heart muscle again and again

A mechanism of this kind is in our opinion a satisfactory explanation of return extrasystoles only but not for the common variety of extrasystoles with accurate coupling Before giving our reasons for this statement it is opportune briefly to discuss the work on which that theory was based

Two observations formed the main basis for the belief that extrasystoles were due to the re entry of the impulse which had produced the preceding that is initiating beat

The first is that a single stimulus applied at the end of the refractory phase may precipitate two or more successive contractions

The first to report such a phenomenon in the heart were Marchand and Munk both in 1878 Marchand found that one make shock applied to the A V border of a frog s hear

produced several contractions increasing in number up to thirty with increasing intensity of the stimulus Munk also in the frog s heart saw a series of pulsations after a single mechanical stimulation and also noticed that the sequence of contractions of the various portions of the heart varied according to the site of the mechanically stimulated part of the heart—an early clear description of an ectopic rhythm Other early observations of several contractions being elicited by one stimulus include those on the bulbus of the frog s heart by Engelmann (1882) also Loven s findings (1886) that a single induction shock applied to the auricle of the frog s heart yielded two or rarely three contractions provided the stimulus was timed to fall within 0 1 second after the maximum of systole the period lasting about 0 1 second during which this phenomenon occurred Loven called kritische Periode (critical period) a term which was to gain increasing importance with the investigations of Wiggers and his collaborators more than fifty years later (*see* below) Tigerstedt and Strömberg (1888) observed in the sinus of the frog s heart long series of contractions resulting from one electrical stimulus applied during the first third of diastole Gaskell observed that one mechanical stimulus applied to the A V ring of the frog s heart may precipitate a series of contractions Andrus s observation of a—presumably heterotopic—auricular rhythm following one forced auricular contraction in certain circumstances may be another instance

The first to consider this phenomenon to be due to a kind of re entry of the impulse and to consider the possibility of its being responsible for extrasystoles seems to have been Mines (1913 1914) The phenomenon of several contractions following one stimulus was extensively studied by de Boer (1921) and his observations were confirmed on the dog s auricle under vagal stimulation by Lewis Drury and Iliescu De Boer was the main protagonist of the conception that extrasystoles are due to a re entry a kind of short circulation of the impulse of the initiating beat From his observations he drew far reaching conclusions extending to the mechanism of flutter and fibrillation as well as to that of extrasystoles All these arrhythmias he considered to be due to a circus movement or a mechanism akin to it This conception was based *inter alia* on the assumption of islets with abnormally long refractory periods where he believed the excitation wave became temporarily arrested while at the same time still being capable of exciting other neighbouring structures The result of all this was thought to be a return of the excitation to a point whence it had started and which had become excitable again Valid objections against this theory were soon put forward summarized in detail by Wenckebach and Winterberg (1927 p 537) and by Rothberger (1931 p 680)

While it would be futile to discuss in detail the objections against a theory which can now have only historical interest mention of it had to be made as the observations themselves can now be understood and explained on entirely different grounds based on more recent physiological work namely repetitive response of a centre to a single stimulus in certain experimental conditions (*see* below in this chapter) Nor is it necessary any longer to assume that this phenomenon is dependent on some pathological condition of the heart such as cooling anaemia effect of poisons vagal stimulation (for refs see Lewis 1925 p 394) since it was subsequently demonstrated that the only essential condition for a stimulus to evoke a repetitive response in the heart is its timing during the critical or vulnerable period of late systole or early diastole (Wiggers and Wegria Moe Harris and Wiggers)

A circus movement based on the assumption of a different and more specific kind of block was considered a somewhat more plausible explanation for extrasystoles with fixed coupling by Ashman and Hull (1945) This view is based on Schmitt and Erlanger s observations on unidirectional block discussed in the section on Return Extrasystoles (*q v*) Applying their findings obtained in strips of ventricular muscle Schmitt and Erlanger postulated an area of depressed conduction in an ultimate twig of the conducting system

there producing locally unidirectional block in the direction from conducting system to myocardium In such circumstances the excitation wave is assumed to enter the nearby myocardium from the penultimate twig only by other branches but be conducted backwards through the affected twig If during that time the adjacent myocardium had become excitable again the excitation wave could then produce a second contraction Ashman and Hull base their views on the above findings of Schmitt and Erlanger While such a mechanism cannot be disproved just as in our opinion it has not been proved we do not consider it an acceptable explanation for the common variety of extrasystoles for various reasons Of these the most important one will become apparent in the succeeding parts of this chapter namely that the mechanism which we put forward is supported by a wealth of physiological observations on the initiation and conduction of impulses in various tissues including the heart whereas the assumption of a circus movement based on that of a hypothetical area of unidirectional block is based only on findings in very special experimental circumstances obtained on strips of cardiac muscle and then without any further proof applied to the most peripheral branches of a highly specialized tissue that is the Purkinje strands The observations of Schmitt and Erlanger can themselves be interpreted in other ways without postulating a circus movement according to Bozler (1943a) the second contraction is due to after discharge that is to impulses arising from the negative phases of the afterpotential Bozler s work is discussed in more detail below (p 512)

Other difficulties are mentioned by Ashman and Hull themselves and we do not think that their explanation of such difficulties is wholly convincing In particular their statement that the island of depressed tissue need not be very large and that therefore the premature beat produced by the mechanism favoured by them would appear as if it originated in a focus seems to us to evoke an unjustifiable assumption if the assumed area of depressed tissue is so small that origin in a focus of the extrasystole appears to occur it seems far more likely to base the explanation on such focal origin This is what we propose to show as actually occurring Our view is also supported by more recent observations on the effect upon extrasystolic impulse formation of warming or cooling of the focus of origin in such instances in which true extrasystoles were elicited by the topical application of various compounds it seems most unlikely that such application creates an area of unidirectional block which responds invariably and instantaneously to warming and cooling of the focus in the way which is described in various places of this book Also the action of the systemic exhibition of drugs and of emotional factors upon extrasystoles is far more likely to be due to the effect of such factors upon the local conditions of the ectopic focus known to be susceptible to nervous influences and to be unstable than to an influence on a (hypothetical) area of unidirectional block This too will we hope become apparent in the course of the subsequent parts of this chapter

The second observation assumed by Lewis (1925) and Wenckebach and Winterberg (1927) to support the theory of a re entry mechanism being responsible for extrasystoles is at first sight more convincing It concerns an observation of Lewis Feil and Stroud who noticed in the dog s auricle that after stimulation by rapid induction shocks some after effects in the form of flutter often extended beyond the end of stimulation In one experiment such after effect consisted of one beat only which was followed by a short period of coupled beats (auricular bigeminy) These authors argued that if the one beat constituting the immediate after effect was auricular flutter reduced to one beat and thus due to a re entry the subsequent ectopic beats of the bigemini should be due to the same mechanism

A similar observation was made in a dog by Scherf (1926) illustrated by Fig 202 Both vagi as well as the right sympathetic had been cut and the sinus node had been eliminated by clamping The prevailing rhythm was A V rhythm with preceding activation of the auricles (diphasic P waves and a P R interval of 0 06 second) As the result of stimulation of the right auricle by rapid induction shocks a series of auricular ectopic beats

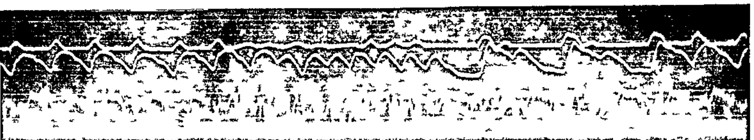


FIG 202 —From an experiment on a dog Tracings from above downward signal (stimulation) suspension curves of right auricle and right ventricle electrocardiogram (ano oesophageal lead) time base 0 02 second For explanation see text From SCHERF 1936 *Z ges exp Med*

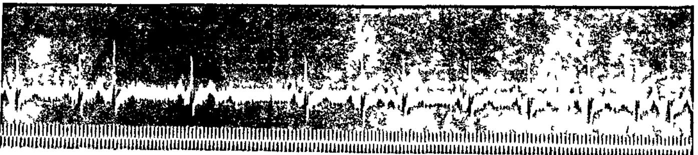


FIG 203 —From a woman of thirty six with attacks of paroxysmal tachycardia Note after the third sinus beat two P waves at an interval of 0 2 second Time base 0 04 second For further explanation see text

occurred After the end of this auricular tachycardia the P R interval was lengthened from the previous 0 06 to 0 08 second The first two A V beats were followed by two premature P waves the third one by only one the interval between the two P waves following in short succession corresponding to a rate of 650 per minute (The auricular contractions corresponding to those P waves can also be traced in the suspension record) The shape of these P waves resembled that of some of those occurring during stimulation and if more persistent flutter occurred in this experiment it showed P waves of the same shape Later similar arrhythmias were obtained by the topical application of aconitine or acetylcholine

A comparable tracing was recorded in a clinical instance (Fig 203) The patient a thirty six year old woman without any evidence of structural heart disease suffered from attacks of paroxysmal auricular tachycardia flutter and fibrillation In Fig 203 several auricular extrasystoles are seen some of them occurring early in diastole and showing aberrant intra ventricular conduction Following the third sinus beat two premature P waves were recorded the first of which is superimposed on the T wave of the preceding beat The interval between these two P waves is 0 2 second corresponding to a rate of 300 per minute Here again the mechanism underlying the origin of these two P waves occurring in quick succession can be considered to be rudimentary flutter

While we believe that such arrhythmias are in fact rudimentary flutter we do not think that they can be interpreted as being due to a circus movement The argument of Lewis and of Wenckebach and Winterberg was since flutter is due to a circus movement and since the above arrhythmias are rudimentary flutter down to one ectopic beat of a bigeminal group such ectopic beats must therefore also be due to a circus movement As however for reasons fully discussed in the sections on flutter and fibrillation we believe flutter to be due not to a circus movement but to a repetitive impulse formation in an ectopic centre the above reasoning of Lewis and of Wenckebach and Winterberg has been deprived of its basic rationale and we interpret the instances of rudimentary flutter described above as due to ectopic focal impulses

In addition to this there are valid objections against the assumption of extrasystoles being due to a circus movement Apart from those discussed above in connexion with Ashman and Hull s views the length of coupling of some extrasystoles particularly of auricular ones is a great stumbling block which was also realized by Lewis (1925) he pointed out that there is no path in the auricles of sufficient length for a circulating wave of excitation to move during such interval—and such continuous movement is of course a *conditio sine qua non* for assuming such a mechanism

IMPULSE FORMATION IN AN ECTOPIC CENTRE

If our contention that auricular flutter and fibrillation are due to the rapid stimulus formation in a single centre or several centres respectively is correct a closer resemblance of these arrhythmias to extrasystoles would be established than had hitherto been assumed For one of the more important conclusions of earlier studies on extrasystolic arrhythmias was that extrasystoles originate in a circumscribed focus The foundation of this view—which also made it possible to exclude re entry (or circus movement) mechanism regarding extrasystoles—warrants some more detailed discussion

The Origin of Extrasystoles in One Circumscribed Focus

The fact that extrasystoles may originate in *one* circumscribed focus was experimentally demonstrated in the following way

In experiments on the dog s heart *in situ* it could be shown that after the injection of quinine for the purpose of avoiding ventricular fibrillation electric shocks applied to any



Fig 204 —From an experiment on a dog Significance of the individual tracings as in Fig 202 For explanation see text From Scherf 1926 *Z ges exp Med*

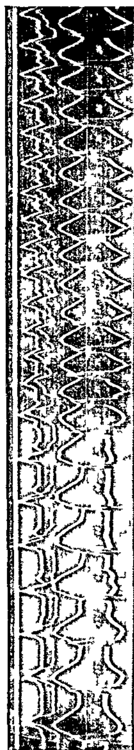


Fig 205 —From an experiment on a dog Tracings from above downward Signal (stimulation) suspension curves of right auricle left auricle right ventricle electrocardiogram time base 0 02 second Re appearance of ectopic beats at a greatly increased rate resulting from warming their site of origin For further explanation see text From Scherf 1927 *Z ges exp Med*

part of the ventricular surface caused series of ectopic beats to occur after the end of stimulation The additional administration of small doses of barium—too small to cause any changes in the electrocardiogram—facilitated the onset of such ectopic arrhythmias

Fig 204 was obtained from a dog anaesthetized with ether shortly after the injection of 0 2 gramme of quinine As the left bundle branch had been severed the ventricular complexes of the first two beats show the typical bundle branch block shape Four ectopic beats were elicited by stimulation of the right ventricle with induction shocks *(The first coincided with a sinus beat and showed a combination complex of almost normal shape)* Following these four forced beats a series of seven consecutive abnormal complexes were observed having a similar shape and assumed to originate in the previously stimulated centre *Such series were occasionally much longer,* comprising as many as thirty beats (Scherf 1926)

The view that such ectopic beats originated in the stimulated centre was strongly supported by the observation that warming the site of former stimulation resulted in an increase in rate of the ectopic beats Fig 205 is taken from such an experiment A long series of ectopic beats had occurred in a dog sensitized with barium after electrical stimulation of a circumscribed area on the surface of the right ventricle Fig 205 shows the last three ectopic beats of this series followed by four beats of the basic (A V) rhythm subsequent *warming of the ectopic focus brought out again the ectopic rhythm with an increased rate* (Scherf 1927)

More recently it has been found that extrasystoles with accurate coupling can experimentally be produced by the focal epicardial application or sub epicardial injection of solutions of barium or sodium chloride or of digitalis (see appropriate sections) As is pointed out there such experiments tended to show that the extrasystoles originated in a circumscribed focus namely the site of application of the compound Here it may be added that the instantaneous suppression of the extrasystoles by cooling the site of origin and their immediate appearance by its warming in certain experimental conditions are further observations which make the assumption of a local circus movement most unlikely to say the least *(see* Scherf 1942) Fig 206 reproduces some relevant observations

Fig 206a is taken from an experiment in which a 10-per cent solution of sodium chloride had been injected sub epicardially into a small area of the conus of the right ventricle While this injection alone did not produce any arrhythmia the recorded bigeminal action ensued immediately on warming the site of injection by a thermode

Fig 206b illustrates the converse phenomenon focal application of 0 1 cc of a 0 1 per cent solution of ouabaine to the apical region of the left ventricle had yielded the arrhythmia reproduced at the beginning of the record namely two or three left ventricular extrasystoles following each sinus beat Cooling of the site of application immediately abolished the arrhythmia (second part of the record) This phenomenon could at will be reproduced several times

Fig 206c shows in its first portion auricular bigeminy The sinus beats are characterized by *tall peaked P waves each is followed by an auricular extrasystole the P waves of* which are much smaller This arrhythmia had been elicited by the subepicardial injection of strophanthin into a small area over the middle portion of the sinus node While it was present, strophanthin was sub epicardially injected into the conus area of the right ventricle This second injection alone did not cause any change in the arrhythmia but warming of its site invariably precipitated a ventricular tachycardia originating there Such an instance is shown in the latter portion of Fig 206c Beginning and end of warming are indicated in the record by arrows, the ventricular tachycardia started two seconds after the beginning and terminated 1 6 seconds after the end of warming

The production by means of barium strophanthin and aconitine of various forms of arrhythmias including bigeminy, in isolated strands of Purkinje tissue (Wachstein) may

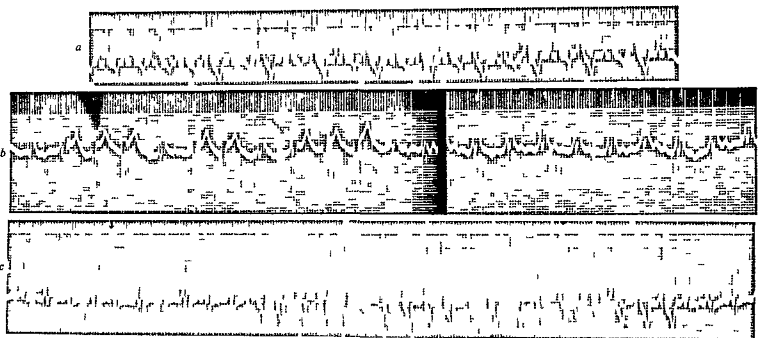


FIG 206 —From experiments on dogs *a* Bigeminal rhythm precipitated by warming the site of sub epicardial injection of sodium chloride (conus of right ventricle) *b* The first part of the record shows two or three left ventricular extrasystoles precipitated by the focal application of 0 1 cc of a 0 1 per cent solution of ouabaine to the apical region of the left ventricle The second part of the figure shows abolition of the ectopic arrhythmia by cooling the site of application of ouabaine *c* The first part shows auricular bigeminy elicited by the sub-epicardial injection of strophanthin into the middle portion of the sinus node The later part of the figure shows a right ventricular ectopic tachycardia precipitated by warming the site of the previous sub epicardial injection of strophanthin into the conus area of the right ventricle Beginning and end of warming indicated by arrows For further explanation see text

briefly be mentioned as further supporting the view that such contractions originate in a circumscribed focus

The Dependence of Extrasystoles upon an Initiating Beat

While the investigations discussed so far demonstrated that ectopic beats arise from a circumscribed focus they did not provide any information as to the mechanism underlying the common variety of extrasystoles with fixed coupling The essential difference between the above experimental and the clinical arrhythmias was that in the former ectopic beats were elicited by some local experimental interference and—with the exception of those due to the topical application of certain compounds—were not accurately coupled to the preceding beat whereas in the latter the extrasystoles follow the initiating beat with accurate coupling and without any artificial localized stimulation The argument was therefore always possible and perhaps justified that the above experimental arrhythmias were due to increased automaticity of an ectopic centre and that conditions prevailing in such arrhythmias were qualitatively different from those in true extrasystolic arrhythmias about the nature of which they did not yield any conclusive information

This problem became accessible to experimental investigation when it was found by Scherf in 1929 that true extrasystolic arrhythmias could experimentally be produced by means of the systemic application of aconitine This made it possible to show that extrasystoles are caused by the preceding beat Such arrhythmias resemble in every way the common clinical variety the extrasystoles having in the electrocardiogram constant shape and accurate coupling to the preceding beat Arrhythmias of this kind are produced by aconitine only if this is given in a special way the details of technique being described in the chapter on Extrasystoles and the Nervous System (*see* p 255) All authors who had previously studied arrhythmias caused by aconitine obtained only irregular ectopic arrhythmias soon changing into ventricular fibrillation if bigeminal rhythm occurred at all it extended only through a few cycles This fact deserves to be briefly mentioned in view of some misleading statements recently made in this connexion See section on Flutter and Fibrillation p 228

If aconitine was administered according to the method published by Scherf (1929) not only isolated extrasystoles but also long chains of bigeminal heart action due to extrasystoles could be produced this made it possible to demonstrate that the extrasystoles were precipitated in the ectopic centre by the preceding beat and were not due to an independent automaticity of the centre This was shown in several ways

(1) If during a continuous bigeminy a forced (ventricular or auricular) contraction was elicited by a mechanical or electrical stimulus such forced contractions were followed by the same extrasystoles as were the normal beats before such stimulation

Fig 207 illustrates this condition As a result of aconitine action trigeminal rhythm was present one sinus beat being followed by two ventricular extrasystoles arising in the left ventricle On two occasions (the fourth and the tenth beat of the record) a forced beat of the right ventricle was precipitated by mechanical stimulation and these were followed by the same couple of left ventricular extrasystoles as were the sinus beats With manifold variations of this experimental procedure it could be shown that whenever during bigeminal or polygeminal rhythm a forced beat was elicited it was invariably followed by the same extrasystoles as were the sinus beats Irrespective of where such forced beats were produced whenever their excitation spread over the heart they precipitated extrasystoles in the same centre of extrasystolic impulse formation

(2) In addition to the constancy with which such forced beats precipitated extrasystoles the length of the coupling could be shown to depend in an analysable way on the length of the path which the initiating impulse had to traverse in order to reach the centre of

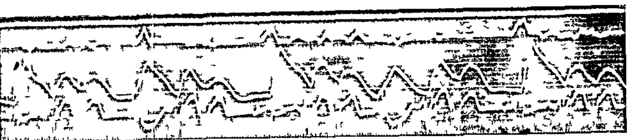


FIG 207.—From an experiment on a dog Significance of the individual tracings as in Fig 202 Trigeminal rhythm due to a ontine one sinus beat being followed by two left ventricular extrasystoles The fourth and tenth beats are ectopic beats precipitated in the right ventricle by mechanical stimulation These forced beats are followed by the same couple of left ventricular extrasystoles as are the sinus beats The length of the coupling of the first extrasystole depends on the site of origin of the preceding beat For further explanation see text From SCHERF 1930a *Z ges exp Med*

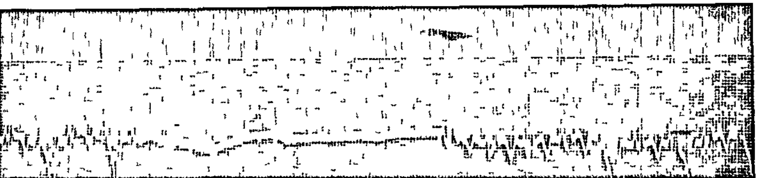


FIG 208.—From an experiment on a dog Lead 2 The beginning of the tracing shows bigeminal rhythm due to the topical application of 0 05 cc of strophanthin into the conus area of the right ventricle Faradic vagal stimulation produced cardiac standstill without any automatic beats From SCHERF 1944 *Exp Med Surg*

extrasystolic impulse formation thus proving that impulse formation in this centre does in fact depend on an initiating beat This is illustrated by the same Figure 207

Extrasystoles experimentally produced by aconitine have an absolutely constant coupling as long as they follow the same kind of initiating beat If however the site of origin of the initiating beat varies the length of coupling of the extrasystoles varies in a systematic way *Thus in Fig 207 the coupling of the first extrasystole following* a sinus beat was invariably 0 31 second as compared with 0 35 second of those same (left ventricular) extrasystoles following beats forced from the *right* ventricle If in the same experiment beats were forced in the *left* ventricle the coupling of the extrasystoles after such beats was 0 29 second In this experiment the extrasystoles always originated in a focus in the left ventricle whenever they followed a beat forced in the contralateral ventricle their coupling was 0 03–0 04 second longer and when following a forced beat of the ipsilateral ventricle was 0 01–0 02 second shorter than the coupling of those premature beats which followed sinus beats This observation indicates that the length of the coupling depends *inter alia* on the length of the path which the initiating impulse has to traverse in order to reach the extra systolic centre (Scherf 1930 a) The difference in the lengths of coupling accords well with the interval required for an impulse to spread from one ventricle to the other (Eppinger and Rothberger Lewis and Rothschild) Similar observations regarding the length of the path of an impulse being responsible for the interval between two contractions were made by Bethe (1937) on strips of the umbrella of medusae (Cotylorhiza)

(3) If during bigeminal rhythm due to aconitine bundle branch block lesions were produced similar systematic and analysable changes in the coupling of the extrasystoles were seen Such observations described in the chapter on Coupling (p 195) led to *the same conclusions as set out under (2)*

Extrasystolic and Automatic Impulse Formation

The work reviewed so far can be said to have established that extrasystoles are pre cipitated by the preceding beat that they originate in a circumscribed focus and that they are not due to re entry (circus movement) of the initiating impulse

The question can now be discussed whether extrasystoles are due to increased auto maticity of the ectopic centre or whether as we believe extrasystolic impulse formation should be separated from the automatic one This problem may be approached from two different angles a critical review of the arguments put forward to claim an identical mech anism and observations supporting the separation of extrasystolic from automatic impulse formation

The first approach has already been discussed earlier in this chapter under the heading of Extrasystoles and Parasystole For co existence of an ectopic *automatic* centre of impulse formation with a normal pacemaker is the hallmark of parasystole and it was stated above as well as in the chapter on Pararrhythmias that attempts were made to explain, by such mechanism extrasystoles with accurate coupling Reasons were given why this view is untenable and the arguments need not be repeated here which preclude the application of a parasystolic mechanism to the explanation of extrasystoles

The second approach refers to observations on true extrasystoles which showed absence of increased automaticity thus supporting the distinction between these two forms of ectopic impulse formation

One impressive example is contained in the experimental investigations of Goldenberg and Rothberger (1931) on strophanthin arrhythmias In experiments on dogs arrhythmias were produced by the intravenous injection of strophanthin combined with the inhalation of a mixture containing 25 or 30 per cent CO_2 in O_2 By this technique various ectopic arrhythmias could be produced including bigeminal rhythm with accurately coupled

extrasystoles polygeminy and ectopic tachycardias If in such experiments the vagus was stimulated the result was cardiac standstill through several seconds (in one experiment 14 06 seconds!) during which only very occasional idioventricular automatic beats were observed which usually had a shape different from that of the extrasystoles This observation proves that there was no vestige of increased automaticity of the ventricles in conditions where extrasystoles were numerous and that therefore these two forms of ectopic beats must be due to separate mechanisms Such suppression of ventricular activity by vagal stimulation *cannot of course* be a *direct* vagal effect for it is known that in the mammalian heart such vagal influence does not extend to the ventricles These same experiments of Goldenberg and Rothberger contain a further proof of this if proof were needed for vagal stimulation was of no effect if applied during an ectopic tachycardia and produced standstill only *after its termination that is by inhibiting the next sinus beat With the suppression* of the sinus beat the extrasystoles also failed to occur thus proving their dependence on an initiating beat A similar observation was made by Schott in rabbits

Another convincing example was found in experiments on arrhythmias following the *topical application of strophanthin by means of sub epicardial injection* (Scherf 1944) As pointed out in the section on Digitalis by this method extrasystoles originating at the site of the injection can be produced As distinct from ectopic arrhythmias following

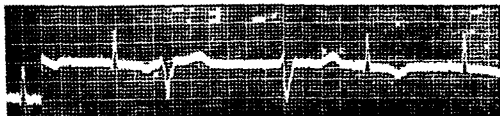


FIG 209 —Lead 1 A ventricular extrasystole is followed by an automatic beat of the same shape

the *systemic* administration of strophanthin those elicited by *sub epicardial* injection have all the characteristics of true extrasystoles Fig 208 is taken from such an experiment The beginning of the record shows bigeminal rhythm which had started five minutes after the injection of 0 05 cc of strophanthin (Strophosid) into the conus area of the right ventricle Faradic stimulation of the right vagus produced cardiac standstill of nearly four seconds during which no signs of ventricular automatic beats were noted After the end of vagal stimulation extrasystoles did not re appear immediately when cardiac action was resumed but only after the fourth sinus beat and then had the same shape and coupling as before

These observations indicate in our opinion that the extrasystolic impulse formation being dependent on and precipitated by an initiating beat should be separated from automatic impulse formation which by definition is independent from any precipitating factor

Occasionally however the same focus may give rise to extrasystolic and to automatic impulses Figs 209 and 210 provide examples

Fig 209 was obtained from a seventy four year old patient with coronary sclerosis The second sinus beat is followed by an extrasystole with a coupling of 0 54 second which after an interval of 1 28 seconds is succeeded by an automatic beat having the same shape as the extrasystole What small differences there are in the features of these two beats are

most likely to be due to the combination of the second complex with a P wave which was due at about that time

Fig 210 illustrates another instance It was recorded in a woman with mitral aortic and tricuspid valvular disease and congestive heart failure The underlying rhythm was auricular fibrillation with frequent extrasystoles having a coupling of 0 40–0 44 second On several occasions the first post extrasystolic beat closely resembles the extrasystole so that origin in the same focus of such two beats has to be assumed The small differences in shape between the extrasystolic and the post extrasystolic (automatic) beats are attributable to the different lengths of the preceding intervals and the varying in superimposition of fibril lory waves The most noteworthy feature of this record is that such automatic beats were on their part sometimes followed by extrasystoles of the same shape their coupling being the same as that of extrasystoles following supraventricular beats (the first two couples of beats in the top and the eighth and ninth beats in the bottom strip) (From Rachmilewitz and Scherf)

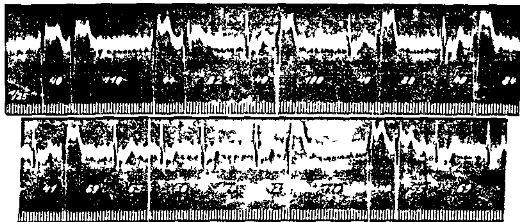


Fig 210 —Lead 3 The two strips are continuous Ventricular extrasystoles and automatic beats of the same shape For further explanation see text From Rachmilewitz and Scherf *Z klin Med*

Similar observations of extrasystoles and automatic beats originating in the same centre were made experimentally (Rachmilewitz and Scherf) and clinically during carotid sinus pressure (Rihl) and during complete A V block (Hoffmann Christian Scherf and Schott 1932 Bloch) A tracing reproduced in a paper by Estape shows this phenomenon in a patient with auricular fibrillation though differently interpreted by the author Such observations as well as the rare transition from parasystole to extrasystoles of the same shape with fixed coupling (*see* chapter on Pararrhythmias p 174) were believed by some to indicate an identical mechanism of these two forms of ectopic impulse forma tion In our opinion this conclusion is not justified Such observations indicate only that there is a focus of ectopic impulse formation which in certain rare instances is capable of both extrasystolic and automatic impulse formation We visualize these two mechan isms to be qualitatively different in a way to be discussed below in this chapter In the great majority of cases of ectopic arrhythmias only one of these two mechanisms is present in the focus In the above instances both these mechanisms exist in the focus at different times the quickest observed succession being found in the two cases of intermittent para systole invariably starting with an extrasystole with fixed coupling described by Scherf and Boyd Furthermore that extrasystolic impulse formation in a centre may predispose

that centre to automatic impulse formation has been known for a long time from observa tions on auricular extrasystoles it is by no means rare that the first post extrasystolic beat has the same abnormal *P* wave as the extrasystole and sometimes this is observed in the first few post extrasystolic complexes (see section on Auricular Extrasystoles p 61)

While there are thus several kinds of observations illustrating a relationship in some cases between extrasystolic and automatic impulse formation it should be emphasized that the total of such observations is very small as compared with the countless instances in which only extrasystoles or only automatic rhythms are encountered

PHYSIOLOGICAL PROCESSES UNDERLYING EXTRASYSTOLIC AND AUTOMATIC IMPULSE FORMATION

If it is desired to formulate some idea about the physiological processes underlying extrasystolic and automatic impulse formation such views have to be consistent with the observations that

(1) these two varieties of ectopic beats mostly occur independently from one another whereby extrasystoles are commoner than ectopic automatic beats or automatic rhythms and

(2) in some comparatively rare instances these two varieties of ectopic beats have been observed to be related to one another in various ways for instance a centre of extrasystolic impulse formation producing at times automatic beats automatic beats being followed by extrasystoles originating in the same focus parasystole changing into extrasystolic arrhyth mia with extrasystoles arising in the same focus

While as stated above in this chapter we fully realize that our knowledge about this subject is very scanty we believe that recent advances particularly in neurophysiology have thrown some light on this complex problem

A few generations ago it may well have seemed heretical to base any concept of cardiac impulse formation on analogies with neuro physiological data at a time when the long controversy between the neurogenic and myogenic theories of the origin of the heart beat seemed at last to have been firmly decided in favour of the latter Of late however the similarities rather than the differences in this respect between heart nerve ganglia and skeletal muscle have tended to be emphasized The following quotations from a recent textbook of physiology are significant in this context An impulse arising in this part of the heart [that is possessing the highest degree of automaticity] will be conducted to con tiguous regions and excite them and will continue to progress in like fashion over the entire heart differing from an impulse passing over a nerve fiber only in the anatomical complexity of the pathways it follows and in the variations in rate of conduction associated with them (Hoff in Fulton p 596) It will be seen that although the heart beat originates in muscle tissues the essential physiological properties of pacemaking myocardial cells which make possible the rhythmic beat of the heart are little if any different from those of nerve fibers nerve cells sense organs and even skeletal muscle fibers which can and under the proper circumstances do act like the pacemaker to set up autogenic rhythms (*Ibid* p 599) Regarding the electrical changes in skeletal muscle Qualitatively and in general outline the muscle action potentials are identical with those of a nerve The mechanism of excitation also is generally held to be essentially the same for muscle and nerve mem branes (Gelfan *ibid* p 116)

Such analogies will we hope become also apparent in the discussion which follows

Some Relevant Physiological Data about Initiation and Propagation of Excitation

This emphasis on the similarity of processes underlying the activity particularly the

a negative after potential A phase of subnormal excitability may succeed which is accompanied by a positive after potential *It is the supernormal phase of recovery with its associated* negative after potential which is of special interest in regard to extrasystoles

The supernormal phase was first found in nerve by Adrian and Keith Lucas (1912) and described as a temporary overswing of the recovery curve of excitable tissue after the transmission of an impulse During this phase—lasting in nerve about 0 015 second—stimuli of an intensity which at any other time would be subliminal become effective Later Adrian (1920) demonstrated the presence of a supernormal phase of recovery in the cardiac muscle of the frog in certain experimental conditions (for example perfusion with a relatively acid fluid) Wastl found it in the fatigued preparation and Eccles and Hoff encountered it occasionally in the pacemaker of decerebrate cats Ashman demonstrated it in the compressed heart of the turtle but Lewis and Master were unable to establish it in the dog s heart More recently Hoff and Nahum found it in the ventricle of fourteen cats anaesthetized with barbiturates while in seven out of nine decerebrate animals it was absent The supernormal phase coincided either with the terminal portion of the T wave or with a U wave when present It is however not proved that the U wave signifies an after potential of the kind of the negative after potential (Schaefer 1942 p 16)

The number of observations indicating the presence of a supernormal phase in man is very small and of the published cases several admit of alternative explanations of the arrhythmia But even the most critical review of the published cases (Mack Langendorf and Katz 1947) had to concede that in five cases a supernormal phase has to be considered present (Luten and Pope Jervell Scherf and Schott 1939 two cases Froment Masson and Gonin Case 1) and to these they added one of their own In others while alternative explanations were preferred the proposed alternatives are in our opinion no more probable than the assumption of a supernormal phase A more detailed discussion of the individual papers dealing with such observations in man would be outside the scope of this book The reader is referred to the quoted paper by Mack Langendorf and Katz but should bear in mind that the explanations favoured by these authors are for some of the cases based on an alternative mechanism suggested by Wolferth (1928) on the assumption that there was no proof that mammalian heart is capable of a supernormal phase this view is no longer tenable Nor does it seem justified to consider supernormality of excitability and that of conduction as separate phenomena as is implied in the quoted paper since the two go hand in hand (Segers 1941 *see also* below) In our opinion a supernormal phase of recovery may well play a greater role in clinical arrhythmias than was thought in the past

One of the earlier experimental studies in which the supernormal phase was considered as one of several factors to account for ectopic arrhythmias is the one by Ashman and Hafkesbring (1925) Using turtle hearts in which the sinus was ligated off they found ectopic rhythms arising either spontaneously or as the result of one sub liminal shock The rate of such rhythms resembling Luciani periods first increased then decreased Ashman and Hafkesbring explained such arrhythmias on the ground of the following assumptions discharge of impulses from an ectopic centre on attainment of a sufficient degree of excitability supernormal phase in the period of returning excitability treppe in excitability for the first several recoveries of a period fatigue of the ectopic focus resulting from its activity and recovery from fatigue during the quiescent periods With increasing rates of electrical stimulation during intervals of spontaneous rhythm the ectopic rhythms occurred at successively later intervals and the groups of ectopic beats became successively shorter until with fast stimulation they became reduced to one single ectopic beat These authors concluded that if the ectopic focus in man was similar to that in the turtle heart it might as permitted by conditions of nerve influences sinus rhythm and degree of supernormal recovery discharge either single ectopic impulses multiple ectopic impulses or series of

impulses producing paroxysmal tachycardia They pointed out that such a focus should not be considered as an automatic blocked off focus but as a potential pacemaker normally responding to every sinus impulse until conditions favour its assumption of the role of actual pacemaker They also emphasized that very gradual changes in the condition of the focus could lead to the sudden onset or end of a paroxysm It will be seen that much of the more recent work particularly on nerve accords well with this view and has brought to light some of the finer mechanism operating in such a focus

Super normal phase and negative after potential are co existing phenomena When the latter is prolonged by fatigue or drugs (for example veratrine) the former is altered in the same way and both are shortened by cooling (Gasser and Erlanger 1930) According to Gasser and Grundfest the association in the mammalian nerve between negative after potential and super normal excitability on the one hand and between positive after potential and sub normal excitability on the other is so close that the curve of excitability should be as characteristic of the nerve and its various states as is the action potential We shall see that the rule holds These authors also found that a second third and fourth negative potential may follow the first one that the play between negative and positive after potentials behaved like damped oscillations and that preparations showing this phenomenon were also subject to spontaneous discharges which increased during the negative and decreased during the positive phases of after potentials It was then shown by Lehmann that alkalinity lowered the threshold and initiated spontaneous discharges when the latter first appeared at a pH of 7 6–7 7 they did so only during the supernormal peried following a maximum spike (1937a) The effect of alkalinity was attributed by Lehmann (1937b) to de ionization of calcium since exclusion of calcium or citrate had the same effect as increase in pH namely lowering of threshold to electrical stimulation and occurrence of spontaneous discharges This explanation was contested by Lorente de No (1947) in whose opinion citrate and oxalate exert their effect by lowering the membrane potential He adduced several reasons why the effect of citrate is unlikely to be due to its immobilizing calcium and established that oxalate does in fact lower the membrane potential namely the L fraction (Lorente de No and Feng)

In nerve poisoned with veratrine however a large and prolonged negative after potential may occur in the complete absence of supernormality and some unknown factor additional to the negative after potential seems to underlie supernormality (*see* Krayer and Acheson)

Erlanger and Gasser (1937) summarized some particulars about these phenomena of which the following may briefly be mentioned supernormality was not found in freshly isolated frog s nerve but developed in the course of the experiment as the negative after potential grew *The end of the relatively refractory period comes earlier but excitability* increases for the same length of time as before and thus the maximum of excitability gets *to be definitely greater than the excitability at rest Supernormal excitability then con*tinues during the progress of the negative after potential and at the same time conduction becomes supernormal in velocity Furthermore these authors point out that in contra distinction to the constancy of the spike and of the absolute refractory period the after potentials are very variable Regarding the significance of supernormality the following sentence indicates its importance in the context of this book Raising the excitability temporarily either from the resting level or an equilibrated subnormal level supplies an excellent mechanism for picking up excitation from a subthreshold background This *they illustrate by the following example which also confirms a similar previous observation* of Gasser and Grundfest a mammalian nerve is stimulated by thyratron shocks at a rate somewhat above 100 per second and at a strength just at threshold for the most irritable fibres If a single shock is added sufficiently strong to excite the whole nerve the subsequent thyratron shocks falling in the supernormal phase—at first of the strong induction shock

subsequently of the preceding propagated disturbance—become supra threshold and this phenomenon repeats itself until a gradually growing positive potential associated with subnormality terminates the response This is a modern illustration of an observation of great importance for the understanding of extrasystoles namely the Wedensky effect

The Wedensky Effect and Allied Observations

In 1886 Wedensky found in the sciatic gastrocnemius preparation of frogs that sub threshold faradic stimulation of the nerve (which did of course not result in any contraction) was followed by a tetanus after a maximal induction shock if this was applied proximally to the site of (continuing) sub threshold stimulation Wedensky s observation was confirmed by several investigators Wassiliew and Mogendowitsch found that this Wedensky effect is enhanced by hypertonic solutions of glucose or NaCl by Ba Ca and Mg reduced by hypotonic solutions of glucose or NaCl by H Li OH' Rb and K Mogendowitsch subsequently established that the application of a moistened crystal of NaCl between the muscle and the site of stimulation (induction shocks) also precipitated the Wedensky effect He made the further important observation that it was immaterial whether the stimulating electrodes were applied proximally or distally of the site of application of the NaCl crystal He offers the following explanation A single excitation which has just arrived in an altered locus there produces a more or less lasting increase in excitability owing to which subthreshold impulses become suprathreshold The single excitation wave can act either direct or by way of ricochet In order for a summation of excitation of the type of a tetanus like single twitch to occur it is not always necessary for the single excitation to pass through the altered locus It is sufficient if it penetrates into the focus irrespective of its position (Our translation)* This observation illustrates one variety of conditions for picking up excitation from a subthreshold background (see above) and also the importance of chemical stimulation in the production of repetitive discharge discussed below (p 507)

Samojloff established that, contrary to Wedensky s interpretation the phenomenon actually is a true tetanus He also made the important observation that the activating effect of the single induction shock lasted through a considerable time It could be demonstrated if the sub threshold stimulation was started as long as 0 2 second after the application of the induction shock and was also present with very low rates of sub threshold stimulation namely as low as two stimuli per second giving an interval of 0 5 second during which the activating effect could be noted Such intervals considerably exceed the duration of the supernormal phase and Samojloff puts forward the explanation that such shocks act through Bahnung (facilitation) at the myoneural junction To a certain extent this explanation is supported by an observation of Denny Brown and Sherrington on decerebrate cats stimulation of a sensory nerve (saphenus) at fifty per second resulted in a reflex tetanic contraction of the M tensor fasciae femoris If in addition another sensory nerve (musculocutaneous) was stimulated with a single shock the existing tetanus increased considerably as long as the stimulation of the N saphenus lasted Other relevant observations (besides those of Gasser and Grundfest and of Erlanger and Gasser already referred to) include those of Dittler and Oinuma on skeletal muscle of the turtle (when the rhythmic action potentials elicited by a constant current had subsided they could be brought out again by one single induction shock) similar observations of Schutz on the effect of direct electrical stimulation upon the contraction and action currents of fully curarized skeletal muscle and certain observations on paraesthesiae in man if such sensation

* Die Erregungssummation vom Typus der tetanisierten Einzelzuckung verlangt nicht durchaus ein Hindurchgehen des Einzelreizes durch die alterierte Strecke Es genugt dazu das Eindringen in den Entstehungsherd unabhangig von dessen Lage

elicited by a constant current was disappearing and already very indistinct one induction shock made the paraesthesiae flare up again for some time (Ebbecke) Similar observations were made by Schaefer and Schmitz a constant current of a certain strength applied to a cutaneous nerve produced a sensation of warmth in the distribution of the nerve if a mechanical stimulus was applied in addition it caused a transient sensation of warmth (apart from the tactile sensation) which was quite different from the effect of the same mechanical stimulation of a neighbouring area These authors draw attention to the analogies between their observations and those of Wedensky and of Denny Brown and Sherrington quoted above

Goldenberg and Rothberger (1933) confirmed the presence of this Wedensky effect on excised Purkinje fibres of the dog stimulated by means of condenser discharges If the fibres responded to near threshold shocks by contraction to only a certain fraction of the applied stimuli single strong induction shocks lowered the threshold so that a 1 1 response ensued for a varying number of such juxta threshold stimuli If sub threshold condenser shocks were used a single induction shock so lowered the threshold that long groups of 1 1 responses followed Spontaneous automatic beats had the same activating effect Applying these findings to clinical ectopic arrhythmias Goldenberg and Rothberger interpreted them as indicating the activity of an ectopic centre located in a branch of the specialized conducting system the impulses of which become effective only during a certain phase of increased excitability consequent upon the preceding beat *

More recently Harris and Rojas concluded that coupled beats observed in the dog s heart after coronary occlusion were best explained as resulting from recovery through supernormality The employment of multiple simultaneous electrograms made it possible to exclude the possibility of a circuitous conduction being responsible for such bigeminy In experiments on cats Hoff and Grant found that with an arterial pH of 7 2 there was no supernormal phase and no spontaneous ectopic beats occurred When by intravenous injection of 4 cc of n/20 HCl the arterial pH was lowered to 7 1 series of ventricular ectopic beats occurred after stimulation and persisted after it was discontinued short bursts of tachycardia and coupled beats were observed When subsequently the administration of acid was slowed and the coupled beats had disappeared a supernormal period was found in that part of the cycle in which the coupled beats had occurred

In a subsequent paper Goldenberg and Rothberger (1935) investigated the effect upon such arrhythmias of localized injury by compression stretching or supra maximal break shocks The result was an increase in rate which the authors attributed to faster depolarization of the centre That stretching increases the rate of depolarization markedly follows from more recent experiments of Scherf Scharf and Goklen which demonstrated that stretching increased the rate of ectopic auricular arrhythmias elicited by the topical application of aconitine If the effect of aconitine had subsided short paroxysms of the tachycardia could be made to reappear by stretching (*see* section on Flutter and Fibrillation) Fig 212 illustrates a left ventricular tachycardia which occurred in a dog during an attempt at cutting the left bundle branch That continuous stimuli may result in rhythmical discharges will be discussed below

The relationship between extrasystoles after potentials and—with some qualifications already referred to (p 499)—enhanced excitability follows even more clearly from experiments with veratrine which is known to produce a marked prolongation of the negative after potential In addition to causing prolongation of systole generally (which may increase from 0 1 to 60 seconds) and of contraction of Purkinje fibres it produces various

* While we would not agree to call such a centre parasystolic as did Goldenberg and Rothberger their views could in our opinion be considered if impulse formation in the ectopic centre was fast otherwise the constancy of coupling of extrasystoles could not be understood The fundamental point in the present context is that these investigations showed the extrasystole to be dependent on a temporary increase in excitability consequent upon a precipitating beat

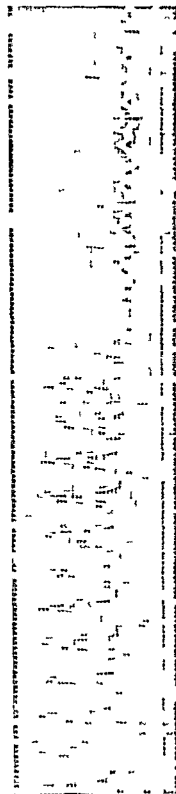


Fig 212 —From an experiment on a dog Left ventricular tachycardia occurring during an attempt at cutting the left bundle branch

arrhythmias in Purkinje fibres which were investigated by Wachstein and more extensively studied by Goldenberg and Rothberger (1936) The latter authors used mechanograms and electrograms Two kinds of arrhythmias were found interferences and oscillations The latter following a large initial contraction were shown by the electrogram to be due to rapid excitations superimposed upon an enormously prolonged after potential They resembled tachycardic attacks having a fixed coupling to the large initial beat and being followed by a pause free from oscillations which resembled a post extrasystolic interval The authors concluded that such oscillations were due to otherwise sub threshold impulses which became effective during the negative after potential More recent work suggests as an alternative explanation that the increased negative after potential is alone sufficient to give rise to spontaneous impulse formation This has been established in various structures the end plate potential in the isolated nerve muscle preparation of frogs may be quoted as one example (Eccles Katz and Kuffler)

Other allied conditions which produce an increase in excitability and may have a bearing on the mechanism of origin of extrasystoles may briefly be mentioned

One such instance is the increase in excitability beyond a nerve block discovered also by Wedensky and commonly known as Wedensky facilitation Such a block can be induced in various ways for example cold drugs or pressure Wedensky (1903) who used various chemicals found that the threshold of the segment below the block becomes lower than it was before If such a block has become complete impulses will not be transmitted through the block zone but as such impulses are stopped at the proximal margin of the block the threshold to electrical stimuli of the nerve below the block is lowered the lowering of threshold being a cumulative and enduring process (Lorente de No 1939) Hodgkin (1937) has shown that this effect upon the excitability of the zone below the block of the stopped impulses is due to the spread of electrotonic current producing an extrinsic potential beyond the block Lorente de No (1939) demonstrated in addition that residual negativity (resembling but not necessarily identical with true after potentials) is also transmitted through a block It seems that such slower changes in residual negativity (spreading over a greater distance than those due to the faster spike like potentials) are related to facilitation of transmission without acting as transmitters themselves

Changes of Excitability and of Potential after Sub threshold Stimulation

Such changes being local ones and closely associated with the local response are more conveniently discussed in connexion with these phenomena (*see* below p 510)

The relevant points in connexion with the mode of origin of extrasystoles of these observations are

A supernormal period of recovery associated with a negative after potential has been found in various tissues and while the extent of its importance in cardiac arrhythmias is still controversial its presence in cardiac muscle has been established During such period of enhanced excitability impulses which at any other time are sub threshold become effective or are formed The after potentials and associated changes of excitability are less constant and more susceptible to environmental changes than the propagated disturbances Such temporary increase in excitability after a conducted excitation must be assumed to play a significant role in the origin of extrasystoles but cannot be the sole determining factor as the activating effect of a conducted beat may considerably exceed the interval during which supernormality can be assumed to be present Nor could the supernormal phase account for the time relations in repetitive responses to a single stimulus which have now to be discussed

Repetitive Response to Continuous Stimuli

Introductory Remarks

The striking resemblance between phenomena observed in Lillie s iron wire model and those in living tissue has often been commented upon an iron wire placed in nitric acid of certain concentrations develops a passive state owing to the formation of a thin layer of oxide If such a wire is stimulated in one of several ways that is if the protective film is locally destroyed temporarily local electrical currents originate which the wire transmits along its length and which can be recorded with a string galvanometer subsequently the passive state of the wire is restored This process of transmission is due to the breakdown and subsequent re forming of the oxide film In certain experimental conditions a *continuous* stimulating reaction in a localized region of the wire—for example contact of the metal with glass—also produces *rhythmical* electrical transmitted changes the rate of which depends on the concentration of the acid after each transmission there is a non transmissive refractory period The analogies with conditions prevailing in the heart are obvious

Another chemical model showing periodicity and rhythmicity which has recently been studied in more detail from the point of view of analogies with biological rhythms is the decomposition of H_2O into H_2O and O in the presence of metallic Hg acting as catalyst (Ernst)

The first observation in living tissue of a repetitive response to a constant stimulus was reported in 1859 by Pfluger who found in the nerve muscle preparation of frogs that constant currents of certain intensities produced tetanus whereas weaker or stronger currents failed to do so He explained this observation tentatively by the extent of the zones of increased and decreased excitability Pfluger s observation was confirmed by several authors (for refs *see* Schriever and Cebulla)

One year after Pfluger Kuhne reported wave like excitations following one another at short distances if a thin muscle with parallel fibres is placed across the electrodes of a chain of galvanic batteries (our translation) (dicht gedrangte wellenartige Erregungen wenn man einen dunnen Muskel mit parallelen Fasern uber die Elektroden einer konstanten Kette legt) This phenomenon has recently been studied in some more detail by Klinghardt including the effect of various ions and of veratrine Rhythmic contractions of

skeletal muscles due to continuous stimulation with faradic or alternating current were described by Fraenkel and by Neuroth (*see also* Bethe 1926 1952 in whose Institute this work was carried out)

The repetitive response to continuous stimuli has been studied in a great variety of circumstances (*see* for example Fessard 1936 Lorente de No and Feng 1946) Earlier in this chapter reference was made to the effect on arrhythmias observed in Purkinje fibres of continuous depolarization of a circumscribed area Altogether the rhythmic response to continuous stimuli is a widespread biological phenomenon the response of the optic nerve to light of sensory nerves to a great variety of continuous stimuli to quote only two instances (*see* also Bethe 1952)

Some other relevant observations have now to be discussed in some detail

Injury

Adrian (1930) recorded in nerves of cats and rabbits the action potentials resulting from injury He distinguished three main types of discharge (1) continuous and regular succession of impulses at a high frequency rarely less than 150 per second (2) an irregular succession at lower frequency and (3) a grouped discharge each group consisting of several impulses very closely spaced and the successive groups following one another at a very low frequency namely ten per second or less Adrian concluded that the detailed arrangement of the continuous and grouped discharges is due to the periodicity imposed by the recovery process of the nerve fibre and that the excitation remains relatively constant over periods which are long compared with the total recovery time of the fibre Regarding the observed grouping of the impulses within the individual groups this could be explained by assuming a steady excitation of gradually decreasing intensity this decrease being due to some opposing change in the tissue *

Electrical Stimulation

The opposing change as postulated by Adrian was considered in more detail in the studies of B Katz (1936) on multiple response to constant current in frog s medullated nerve Katz based his study on Hill s theory of electric excitation by a constant current According to this the applied current rapidly builds up at the cathode a local potential V which is maintained throughout the passage of the current excitation occurs if and when V becomes greater than the threshold U This threshold rises at a rate determined at any moment by the value of V at that moment and by the time constant λ of accommodation the opposing factor of Adrian During the interval at which V is greater than U repetitive responses may be expected to occur at intervals determined by the refractory phase The length of the interval during which repetitive responses can be expected will be greater the slower the accommodation that is the greater the value of λ Katz found the results of experiments in accordance with theory in nerves of cooled frogs repetitive response to constant current of slightly more than rheobasic strength was observed and in such conditions accommodation was found to be very slow λ being at first 300 msec and even after four to six hours soaking at room temperature still being above 100 msec On the other hand interferences resulting in shortening the time of accommodation reduced or abolished repetitive response (for example soaking the nerves in Ca rich solution) The widely studied effect of the reduction or removal of Ca in inducing repetitive response and spontaneous activity was found by Katz to be associated with a great increase in the time constant λ of accommodation and a considerable lowering of threshold These

* Injury potentials were considered to be one of several factors in the origin of ectopic beats after experimental coronary occlusion (Harris) and are held to account for ectopic arrhythmias which occur during cardiac catheterization

observations emphasize the importance of the ionic milieu and are related to investigations on chemical stimulation discussed below

According to Schriever and Cebulla the process termed accommodation is more complex and it is the gradient of current necessary to excite which varies in a characteristic fashion according to whether the response is non rhythmic or rhythmic

Erlanger and Blair s studies (1936) on repetitive responses in the phalangeal nerves of frogs bring out several features of importance in connexion with the mode of origin of extrasystoles In these investigations *stimulation by means of rectangular currents* was used While the usual response of the excised frog s nerve consists of a single action potential repetitive responses were observed in a variety of conditions These authors point out that repetition induced by rectangular current is characterized by its unpredictability and that if a fibre repeats it does so only when the current is applied to more or less definite loci of the fibre Repetition was found to be rapid (with rare exceptions) and was either immediate or delayed Regarding the latter the interval between closing of the current and the beginning of the repetition is longer it may be very much longer than the sum of the utilization period and the conduction time involved Delay as long as 0 2 second was observed though no effort has been made to determine the limit It is noteworthy that such figures are of the order of length of coupling of extrasystoles (Regarding the mechanism underlying such long periods *see* below local response) Even if repetition gradually failed the repetition pattern as obtained from a fibre at a given point usually remained constant —another analogy to extrasystoles Anodal polarization was found to be of great importance *in maintaining repetition and in determining its character its mode of action in this* respect is twofold (1) at the anode of a continuous current the nerve is in a condition in which it is not readily subject to cathodal depression and (2) the high pH makes for recovery through a supernormal phase Anodal polarization was achieved by using the same electrode as anode of the polarizing and as cathode of the stimulating current Applied in this way anodal polarization converted immediate into delayed repetition and increased somewhat the number of responses It was also found that by anodal polarization the correlation between changes in excitability and repetition could be greatly improved to such an extent that the authors came to the following conclusions that fibers that have exhibited delayed repetition but which were not being subjected to artificial anodal polarization either were anodally polarized presumably by local demarcation currents *or else were subject to some other condition which produces a state similar to the anelectrotonic state*

These findings namely the importance of local demarcation currents or of a condition producing a similar effect may well be applicable to the mode of origin of some instances of extrasystoles The importance of anodal polarization in the production of fibrillation of the dog s heart (Harris and Moe) is referred to in the section on fibrillation (p 231) Moreover amongst the data which Erlanger and Blair discuss in connexion with the exact site of origin of repetition is the observation of Schaefer and Schmitz that an action potential passing into an injured locus may initiate an after discharge there In nerve muscle preparations of frogs Schaefer and Schmitz investigated by means of an oscillograph the changes in the action currents which occurred if the excitation had to traverse a portion of nerve *injured by compression* The *nerve was stimulated by induction shocks of threshold* strength These authors found that the previously smooth curve of the action potential was after injury followed by a series of small oscillations at intervals of 0 5–1 msec lasting 10–20 msec A similar phenomenon was observed if the excitation had to traverse a locus which was strongly polarized anodally here the action potential became strongly deformed in its descending portion and showed numerous waves indicating that numerous action potentials had become superimposed on the otherwise uniform action potential The arriving excitation precipitates new individual discharges Before the arrival of the

action potential the locus in question of the nerve was quiescent as shown by the oscillogram (our translation) *

While Erlanger and Blair reject this mechanism as explanation for their findings it seems to us that it may well be of importance in the mode of origin of extrasystoles This opinion is based *inter alia* on the following observation by Arvanitaki (1937c) A small area *a* of a nerve fibre is anodally polarized or subjected to warming (that is interferences lengthening the after potentials) One of two recording electrodes is placed on *a* the other at a distance at *b* The nerve is electrically stimulated beyond *b* with juxta threshold currents In these circumstances an impulse coming from *b* and conducted to *a*—called afferent impulse —is followed by a large after potential at *a* which there *initiates a spike which is conducted from a to b called efferent impulse* It was also found that the changes precipitated at *a* by the afferent impulse are an essentially graduated phenomenon which is capable of summation (*see* also below local response) If the temperature at *a* was gradually raised the after potentials gradually increased and repetitive responses occurred The same repetitive response could also be observed if the afferent impulse did not actually reach *a* but was blocked in its neighbourhood These observations demonstrate the importance for precipitating an ectopic impulse of anodality (or allied conditions *regarding after potentials) of the ectopic centre as well* as the fact that the initiating impulse need not actually reach the ectopic centre

Similar observations were made on strips of the heart of the tortoise by Segers (1940) Strips of 10 cm length were suspended in two compartments A and B which were separated by a partition a hole in which allowed the strip to be put through Such preparations did not show spontaneous contractions Addition in A of two or three drops of a 1 per cent solution of adrenaline alone did not cause any activity but after sufficiently long electrical stimulation of the end of the strip in A a series of about ten spontaneous contractions occurred which lasted beyond the end of stimulation If the strip was stimulated at its end B the forced beat was propagated to A but after the end of stimulation a series of spontaneous contractions occurred in A which were propagated towards B Segers concluded Le battement rythme spontane de l extremite A apparait comme consequence de l activite provoquee a ce niveau par les ondes d excitation physiologique provenant de l extremite B celles ci determinent donc la meme reaction consecutive que la stimulation electrique de *l extremite A elle meme With sufficient adrenaline added in A one excitation elicited* in B precipitated a contraction wave travelling from B toward A followed by a second wave in the reverse direction Similar effects were seen with CaCl and $BaCl_2$ (applied in A) such repetitive or reflected contractions were suppressed by K or yohimbine Segers attributed such after reactions to the negative after potential acting in the manner of a catelectrotonus

More recently Dawes and Vane studied repetitive discharges in the isolated auricle of guinea pigs They stimulated the preparation by means of square constant current pulses at a rate slightly greater than the normal rate every fourth stimulus was followed at a predetermined time interval by a test pulse of similar form and duration but variable strength They found that if the test pulse of adequate strength fell just outside the absolute refractory period the auricle not uncommonly responded by repetitive discharges varying in number between two and ten and occurring at a frequency much greater than that of normal beats up to 15 per second Spontaneous discharges sometimes continued for a long time up to one hour *These authors assumed that such discharges originated from the neighbourhood* of the stimulating electrode and may be due to persistence of a supernormal period

To revert to Erlanger and Blair s studies amongst the conditions listed as accessory to the initiation of induced repetition is the rise in excitability responsible for the treppe

* Die ankommende Erregung gibt den Anstoss zu neuen Einzelentladungen Vor Ankunft war die betreffende Nervenstelle wie das Oszillogramm zeigte in Ruhe P 168

phenomenon Regarding this the following observation is described In one experiment a rectangular current which was just below the repeater threshold occasionally stimulated one or more axons on breaking Whenever a break response occurred the next application of the constant current and several of the succeeding ones resulted in bursts of repetitions appearing when the rectangular current was closed but some time after its make—with a long delay in other words We have good reasons for believing that in this preparation the increase in excitability resulting from a single response lasted through a second at least and it is concluded therefore that the repetitive bursts occurring during the rectangular current developed in the treppe that was initiated by the response elicited by the break of the constant current This observation seems to us of importance as being another illustration of a very long lasting increase in excitability following one response

Analysis of the intermissions in a repetitive response showed that they were not due to a block along the conducting path but to oscillatory changes in the recovery curve in particular that the recovery period of a fiber is the first of a continuing series of oscillations in excitability with a period about equal to the recovery period Such changes in excitability were actually found and Erlanger and Blair concluded that the first low threshold point must be equivalent of if it is not actually the supernormal phase The period of such (decrementing) oscillations about 5 msec was of the same order as the period of repetition of the fibre

The findings of these extensive investigations which seem to us most relevant in connexion with the mode of origin of extrasystoles can be *summarized* thus The occurrence in certain conditions of repetitive responses to a stimulus which ordinarily results in only one action potential the repetitive response being confined to certain loci of a nerve fibre or portions of a strip of cardiac muscle the great importance of anodal polarization or a *condition producing a similar effect and thus of local demarcation potentials and of changes* in the ionic milieu in producing repetitive response the possibility of an action potential s passing into an injured or chemically altered locus there setting up new rhythmic action potentials the long delay in the onset of repetition after the precipitating stimulus greatly exceeding utilization time + conduction time (corresponding to coupling) the observation of a very long lasting increase in excitability after a single break response the importance of oscillatory changes in excitability during recovery

Chemical Stimulation

The work considered so far was concerned with rhythmic activities precipitated by injury or by constant current (or single induction shocks or current pulses) Chemical stimulation provides another mechanism of a constant stimulus and the rhythmic activities resulting from this kind of stimulation have been extensively studied (for references on early work see Mines 1908) Several references to the topical application to the epicardium or the sub epicardial layers of various chemical compounds will be found in this chapter as well as in the appropriate sections of the chapter on drugs (sodium barium digitalis) The importance of the ionic milieu in connexion with excitability to electric stimulation has been repeatedly mentioned earlier in this chapter In addition a few investigations warrant a more detailed discussion in the present context

In nerves the application of crystals of calcium chloride or any salt producing a high osmotic pressure precipitated a high frequency discharge (Adrian 1932)

In the nerve of the crab where repetition is easily observed generally it could be induced by a variety of chemicals (Auger and Fessard 1933) Rhythmic discharges were not noted in fresh nerves but by keeping them in sea water for one to two hours this property could easily be elicited (Arvanitaki and Fessard 1934) Besides various inorganic compounds amongst which Na hyposulfite proved particularly efficacious excess of OH (pH about 11) and various alcohols were found effective in this respect (Fessard 1936) The slow

variations of the base line which was found in such experiments in addition to rhythmic discharges will be discussed below in connexion with pre potentials

In numerous investigations partial removal of Ca has been found to favour the occurrence of rhythmic discharges Brink and Bronk (1937) investigated this in the sciatic nerve of frogs By citrate or by reduction in concentration partial removal of Ca was effected at one portion, usually one end of the nerve In such conditions continuous trains of impulses of a frequency of about 100 per sec were observed to originate in the treated region If Ringer s solution was then substituted the continuous train of impulses was transformed into *series of rhythmic volleys that is bursts of impulses following in succession The duration* of such volleys then declined and after a period of transition a fairly constant state ensued during which the duration of the volleys may amount to several seconds or each volley may continue for one or two minutes and recur every ten minutes But even at these longer intervals the volleys and the periods of silence are constant to within a few per cent for an hour or more The authors point out certain similarities between these observations and those made in connexion with injury (Adrian 1930 discussed above in this chapter) and alcohol treated crustacean fibres (Fessard 1936) While we fully appreciate the caution necessary to apply such observations to cardiac arrhythmias we believe that they have a bearing on the mode of origin of extrasystoles in the following respect rhythmic discharges following a continuous stimulus and constancy of volleys and of periods of silence even with longer intervals are features comparable to the constancy of shape and of coupling of extrasystoles which also may be precipitated by some continuous stimulus and may and often do occur at long intervals

In view of the extensive use which has been made of barium salts in the investigations of cardiac arrhythmias Lorente de No and Feng s Analysis of the effect of barium upon nerve with particular reference to rhythmic activity (1946) is of special interest Mention was made earlier in this chapter of Lorente de Nó s working hypothesis that the membrane potential can be imagined to consist of a Q (quick) fraction related to the fast electrotonus and initiation of propagated spike potential and a L (labile) fraction related to the after potentials and excitability Regarding barium treated nerves Lorente de No and Feng point out that in such nerves the L fraction has a high value and since lowering of this fraction is a n cessary condition for spontaneous firing of impulses to occur such spontaneous impulse formation does not regularly take place This however can readily be initiated by the application of a cathodal current which produces repetitive impulse formation This should be considered to be of the nature of Pfluger s tetanus (*see* p 503) and sharply distinguished from the make response In all instances the tetanus began when the slow component of the catelectrotonus *i e* the decrease of the L fraction of the membrane potential reached a certain level (p 448) During the flow of the applied current *the rhythmic firing passed through a maximum and then decreased to a lower intensity* this is attributed to the fact that the catelectrotonus during the flow of current passes through a maximum and then decreases but does not become low enough to allow a sufficiently high level of the L fraction of the membrane potential to be restored for the firing to be abolished If however the nerve is kept in an atmosphere containing 5 per cent CO_2 the decrease of the catelectrotonus is usually sufficient to prevent rhythmic activity altogether during the further flow of current this being due to the property of CO_2 to increase the L fraction of the membrane potential This is an interesting counterpart to the observations of Scherf (1930b) that in dogs inhalation of a mixture containing 20 per cent CO_2 abolished extrasystoles elicited by aconitine and of Friedberg and Levinson (1931) that the same gas mixture abolished ventricular ectopic tachycardias precipitated by barium (*see also* sections on aconitine and on barium)

Regarding the effect of conduction of impulses on the rhythmic firing during the negative after potential Lorente de No and Feng point *out that this is analogous to a Pfluger s*

tetanus The phenomenon was studied in nerves maintained in an atmosphere of 5 per cent CO_2 and 95 per cent O_2 in which owing to the presence of CO_2 the rhythmic after discharge after a conducted impulse was short In these experimental conditions the repetitive firing after conduction of one volley was hardly detectable increased with the number of volleys in the train attaining a maximum with trains of 5–10 volleys and then decreasing with increasing length of tetanus to disappear altogether with trains having more than 25 volleys This is correlated with the behaviour of the negative after potential observed with the various numbers of volleys it reached a maximum with trains of 9 volleys but with increasing length of trains above this the rate of recovery of the membrane potential during the descending leg of the spike underwent a progressive increase during the tetanus (p 454)

There is thus an interesting similarity between these neurophysiological findings about the behaviour of barium treated nerves and observations made upon ectopic arrhythmias produced in various ways by barium in mammalian hearts In the instance of barium the beginning of the cardiological observations—1911— preceded the neurophysiological ones by several decades whereas in many other respects neurophysiological work on impulse initiation and conduction is now far ahead of cardiological counterparts These analogies also demonstrate that within limits the application to cardiophysiological phenomena of corresponding observations made on nerves is justified

Another property of barium salts deserves brief mention In addition to producing repetitive firing of impulses they give rise to conduction block in certain experimental conditions (*see also* Feng) and of a peculiar type This association also found with acetyl choline may be of importance to account for the protective mechanism of ectopic centres (*see* p 331)

The extensive studies of Brink Bronk and Larrabee (1946) are of importance in the present context especially from four points of view namely regarding the relationship between repetitive discharges and (1) excitability (2) O_2 consumption (3) potential gradient and (4) local oscillatory changes of potential

These investigations were carried out on nerves of squids and frogs and were concerned mainly with the effect of Ca K and acetyl-choline as chemical stimuli

If the concentration of Ca was lowered below a certain level (0 3 mM in frog 10 mM *in* squid nerves) self initiated trains of propagated impulses started that is the axons tr[illegible] formed the continuous action of a physical or chemical agent into a series of *recurring* events which are made manifest as nerve impulses The frequency of impulses depen[illegible] on the degree of lowering Ca and repetitive activity began after the rheobase had decrea[illegible] to below 5 per cent of its initial value Such impulses usually began at random inter[illegible] and then increased in frequency but sometimes they started with a high initial frequen[illegible] then declined to a lower level the latter occurred usually after a previous period of chem[illegible] excitation that had been arrested by restoration of Ca or during the actual resto[illegible] The former is somehow reminiscent of extrasystoles which so often precede p[illegible] tachycardia originating from the same focus though the analogy breaks down in th[illegible] rare exceptions the rate of the tachycardia does not increase The latter observa[illegible] be likened to the clinical arrhythmia of Extrasystolie a paroxysmes tachyc[illegible] it is assumed that during the decline in frequency of the ectopic rhythm the [illegible] takes over for a few beats

The effect of calcium removal seems complex thus these authors show[illegible] makes a nerve more sensitive to other ions for instance KCl or tetra-et[illegible] chloride

In studying conditions in pre and postganglionic fibres these authors [illegible] response in the synaptic region also could be modified by varying the conc[illegible] When pre ganglionic fibres were stimulated by repetitive electric shocks [illegible]

the cells discharged repetitively but at a much lower frequency which *inter alia* depended on the characteristics of each cell The question poses itself whether, or to what extent conditions of synaptic transmission may be applicable to the mechanism of origin of extra systoles

It was further found that increased rate of oxidation is essential for the initiation of impulses If an oxidation inhibiting agent (sod azide) was applied to the citrate treated portion of the nerve a concentration of azide sufficient to restore oxidation to a normal rate was sufficient to suppress chemical excitation but the Ca deficient and azide treated regions of nerve still conducted impulses produced by electrical stimuli This higher require ment of O_2 for the initiation of impulses as compared with that for their conduction may well have a bearing on the difference in mechanism between automatic and extrasystolic impulse formation The parallelism between O consumption and spontaneous activity was however not present in all experimental circumstances investigated by Brink, Bronk and Larrabee

The effect upon impulse formation of potential gradients applied at the site of Ca removal was investigated by these authors by creating such a potential gradient either chemically or by applying it externally Both methods gave the same results If by increasing KCl in the solution of Na citrate the Ca deficient area was made electronegative to adjacent parts the propagated nerve impulses occurred with reduced frequency con versely if the region was made electropositive to adjacent ones (by sodium thiocyanate) the frequency increased Similarly if the direction of the externally applied current was such that it entered the citrate treated region the average frequency of impulses was reduced for a brief period when the polarizing current was terminated a transient increase in frequency was observed With reversal of the direction of the applied current the opposite changes in the frequency of impulses were observed These observations illustrate the great importance of a combination of chemical factors and potential gradients in initiating trains of impulses and in modifying their frequency The existence of local potential gra dients in the heart has to be assumed in certain circumstances for instance injury potentials the importance of the ionic environment in connexion with impulse formation in the heart has been assumed for a long time The above observations in addition to showing that such assumptions have foundation in fact reveal the mechanism of such factors in some detail

Another observation of Brink Bronk and Larrabee has a considerable bearing on the mode of origin of extrasystoles In giant squid nerves deprived of Ca they found a local oscillatory response of the same frequency as that of propagated impulses which they precede but spikes were discharged only if the local oscillations were of sufficient magnitude If the frequency of the propagated impulses varied it was found that they often did so at rates of simple multiples It could be demonstrated that such longer intervals were due to failure of conducted impulses to be initiated and not due to disturbances of conduction This finding may well have a bearing on the mechanism of exit block (in parasystole see chapter on Pararrhythmias) The similarity of this observation with one of Erlanger and Blair's discussed above will be noted Such local oscillatory changes of potential have been extensively studied in recent years their importance warrants a more detailed discussion

Local Changes of Potential (' Pre potentials ') and Local Response

The discussion so far was concerned with conditions resulting in enhanced excitability after a propagated impulse for example the supernormal phase of recovery and those generally conducive to repetitive response to a single or continuous stimulus Another aspect remains to be considered namely the local processes at the site of impulse formation in their relation to the origin of propagated disturbances and to repetitive responses

The relationship between changes in excitability and those of potentials is discussed earlier in this chapter and the close association between negative (after) potentials and increase in excitability after a propagated impulse was emphasized Similar relations hold good for sub threshold stimuli A momentary increase in local excitability resulting from brief sub threshold shocks was found in 1908 by Gildemeister Bishop confirmed this for sub threshold stimulation with galvanic currents Erlanger and Blair (1931a b) studied in more detail such changes in excitability due to sub threshold constant current as well as to sub threshold induction shocks The relevant points of their results were that during flow of a subrheobasic current directed cathodally with respect to the studied portion of the nerve the excitability at first rises attains a maximum and then falls to a lower but still supernormal level Following the break of the cathodal current the excitability falls from above to below normal The results after a sub threshold induction shock were qualitatively the same Gilson and Peugnet found the behaviour of heart muscle (strips of the ventricle of turtles heart) qualitatively very similar to that of nerve as found by Erlanger and Blair but the time relations as found in frog nerve at 25 C had to be multiplied by about forty for the turtle ventricle Some local also called secondary process was assumed to account for these observations also for the latency to electrical stimulation The study of Rushton (1932) about the excitability of frog s nerve at various instants after the start of a constant current indicated an active local non propagating process at the site of stimulation being additional to the passive electric effect of the stimulus which it activates to produce a propa gated spike (*see also* Arvanitaki 1936 and Newton) These local responses have an electrical sign namely slow potential changes (for a comprehensive description *see* Arvanitaki 1938)

Such slow potential changes preceding the discharge of propagated impulses were found by Adrian (1931) in the ganglia of the water beetle (*Dytiscus marginalis*) and by Adrian and Gelfan (1933) in the sartorius muscle of the frog In the latter the electric changes were recorded at the point of origin of discharges which were elicited by the strictly local application at the site of the exploring electrode of Na citrate tartrate or oxalate It was found that a slow wave of negativity preceding the discharge of the impulse was almost invariable and that at times oscillatory waves of the same order were also observed after the end of a discharge A sustained negative potential associated with repetitive fibre discharges was found in some cardiomers of the gangliionated median cardiac nerve of *Limulus polyphemus* by Heinbecker who localized the origin of this phenomenon in the large unipolar ganglion cells and drew attention to the correspondence of his observations with those of Adrian on the water beetle

In extensive investigations Arvanitaki came to the conclusion that a stimulating (supra rheobasic rectangular) current precipitated the propagated discharge not only passively but that an active local process preceding the spike was set up in addition In crustacean nerves in which rhythmic activity was induced by OH or ethyl alcohol slow negative potentials were recorded which preceded grouped discharges (Arvanitaki and Fessard 1934) The presence of such a process could also be deduced from a study of the latent intervals with currents of different strength and duration The conclusion was that the mechanism by which stimulation was effective consisted of two parts namely one passively conditioned by the current (passive polarization) and another active one which could continue in the absence of continuing polarization (Arvanitaki 1937a b) The main char acteristics of such local changes of potential were found to be they are graduated continu ous of varying speed and while as distinct from the spike they are not propagated they spread along the nerve but with a considerable decrement and are no longer traceable at a distance of 3–5 mm (Arvanitaki 1938 p 27) In this they resemble the spread of elec trotonus All these local slow potentials whether occurring spontaneously or induced were found to have negative and positive components and c est a la variabilite de la resultante

reverse conditions obtain the local response is large, can be produced by shocks which are too weak to elicit any response in normal nerve and turns into a propagated spike at a potential which is lower than that in normal nerve These conditions are illustrated in Fig 213 taken from Hodgkin s paper It seems to us that these findings have a bearing on the mode of origin of extrasystoles for they reveal some of the finer mechanism which may underlie the occurrence of extrasystoles during the supernormal phase of the preceding beat The same holds good for Hodgkin s observations regarding the local response during the refractory period he points out that whereas in a normal resting nerve the response decrements rapidly in the refractory period this tendency is counteracted by the fact that the response is continually working itself into more excitable nerve If the local response encountered suddenly a patch of nerve where the recovery was much more advanced than elsewhere the activity would immediately start to spread faster and the potential would rise

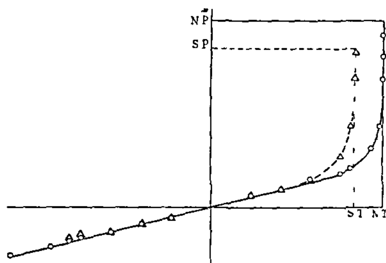


FIG 213 —Broken curve triangles Subthreshold potentials in supernormal period Continuous curve circles Potentials in resting nerve Abscissa strength of shock Ordinate potential measured at 0 47 msec after shock N T and S T are normal and supernormal thresholds N P and S P indicate potentials at which response propagates in normal and in supernormal nerve From HODGKIN 1938 39 *Proc roy Soc B*

steeply in the whole of the cathodic region If the rise in potential were large enough the response would be able to sustain itself by re stimulation and would ultimately propagate throughout the fibre This experiment shows very clearly that there is no fundamental difference between a wave of activity which just succeeds in propagating and one which just fails

If in connexion with extrasystoles a spontaneous impulse formation in the shape of a local change of potential at the site of the ectopic centre is substituted for the artificial subliminal stimulus of Hodgkin s experiments similar conditions may well obtain in cardiac muscle For in view of the constancy in shape and coupling of extrasystoles in the individual case the origin of extrasystoles of the common variety in one circumscribed and constant focus has to be assumed and the presence of islets of temporarily refractory tissue near such focus has often been postulated in connexion with this and other varieties of cardiac arrhythmias

In a more recent study Hodgkin (1948) investigated the local response associated with

repetitive discharges in isolated axons of crustacean nerve (*Carcinus maenas*) Such preparations could be divided into three main groups (1) axons with a recovery cycle showing no significant supernormal phase capable of repetition over a wide range of frequencies (5–150 per second) (2) axons with pronounced supernormal phase this group usually produced trains of impulses of 75–150 per second and was relatively insensitive to changes of the applied current and (3) axons with high threshold which either failed to repeat or did so only if the strength of the stimulating current was much greater than rheobase Only the first two groups will be considered

In axons belonging to group (1) it was found that the local response to sub threshold currents was small as compared with the propagated spike potential for example in one experiment was 6 2 mV whereas the spike potential was 57 mV The response time that is the interval between the beginning of the stimulus and the first spike was very long when the current was weak measuring up to 0 098 second and was of the same order as the intervals between successive impulses in the repetitive train This observation suggests that response time rather than refractory period is the primary factor in determining the frequency of repetition when the current is weak That the repetition frequency was very much smaller than could be accounted for by the refractory phase was observed also with stronger stimulating currents with 5 per cent above rheobase the repetitive responses would have had a frequency of 240 per second if the refractory period had been the sole determining factor whereas the actual rate of repetition was about thirteen per second The refractory period became of importance with strong currents which tended to reduce the response time toward zero but the repetition interval never became less than 6 5 msec Long response time makes not only for a low rate of repetition but also for stable low frequency discharges and it could be shown in confirmation of previous work of Hodgkin and Rushton that a long response time is associated with a prolonged local response Its growth can be very slow indeed in extreme cases taking up to 950 msec This local response is superimposed upon the passive depolarization and a spike potential originates when the depolarization reaches a certain critical level The whole process must repeat before a second spike of a repetitive response occurs and a marked resemblance could be shown between the changes in potential which preceded the first impulse and those preceding any other impulse in the repetitive train Such changes need not be identical because the rate of growth of the local response is exceedingly sensitive to small changes in current strength or excitability and a very slight residue of supernormality or refractoriness may modify it

In axons of group (2) that is those showing a pronounced supernormal phase the frequency of repetitive discharge was comparatively insensitive to changes in the applied current Although supernormality is of importance in accounting for this in this group of axons again this is not the sole factor determining the frequency For instance the repetition rate was 90 per second at rheobase and 150 per second at 2 41 rheobase whereas if supernormality were the sole determining factor it would have been 540 per second Hodgkin explains this by the assumption that during the period of supernormality the local response develops at an increased rate and that therefore the spike arises earlier than it would do in the absence of a supernormal phase But this does not mean that the spike must arise at the height of supernormality it need not originate until after the end of the supernormal period This view is supported by the observation that the development of the local response was much faster during a supernormal phase than it was after the make of the current This accords well with Hodgkin s previous findings regarding the behaviour of the local response and its turning into a propagated spike potential during supernormality (*see* above)

In certain circumstances the rate of growth of the local response may be exceedingly slow and both response time and repetition interval have exceeded 500 msec on certain occasions

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Of the results of these studies those most relevant to the origin of extrasystoles and of ectopic beats generally may be *summarized* thus

Local changes in potential resulting from metabolic changes apparently being a pre requisite for the discharge of propagated impulses influence upon such local changes of potential of the supernormal phase of a preceding spike independence of response time—corresponding to coupling—from the supernormal phase in the sense that the repetitive responses need not arise at the crest of supernormality and that response time as well as repetition interval may be very much longer than the interval during which supernormality can be assumed to exist influence of the ionic environment on the number of repetition and on the setting up of automatic activity at the site of former stimulation the effect upon the local response of refractory tissue with the result that the particular conditions may lead either to a dying out of the local response or to its growth into another propagated spike the observation that small fluctuations in the strength of a near threshold stimulus may produce very great differences in the local response and excitability with the result that no fundamental difference seems to exist between a wave of activity which just succeeds in propagating and one which just fails the possibility that a higher rate in O_2 consumption is necessary for automatic impulse formation in a centre than is necessary for the conduction of an impulse

MECHANISM OF ORIGIN OF ECTOPIC BEATS

If it is attempted to put forward some views about the mode of origin of ectopic beats on the grounds of the work discussed in this chapter it must be stated at the outset that such views can only be tentative Findings obtained in animal experiments can be applied to human pathology only with great reserve Moreover however great the analogies found between the various excitable tissues here again the greatest caution is necessary in applying *findings obtained in one excitable tissue to others All that can be hoped for is to formulate* some ideas which based on more recent advances in physiological knowledge and not conflicting with any known facts provide some satisfactory even if only partial under standing of the experimental and clinical observations

For all ectopic beats activity in a circumscribed centre has to be assumed

Extrasystoles

To consider the common variety of extrasystoles with accurate coupling and constant shape first here the activity has to be located in one single circumscribed focus In those numerous instances in which occasional extrasystoles are observed separated by long periods of an undisturbed dominant rhythm the activity in the ectopic centre must be sub threshold for long periods It seems reasonable to assume that it consists of some metabolic change a fluctuation in resting metabolism which as discussed above has also been assumed to underlie the electrical sign of such local processes namely the local graduated non propagated changes in potential Evidence has been discussed which tends to show that such changes consist either in a gradually increasing negativity or in oscilla tions and that increased negativity is associated with increase in excitability Such activity becomes supra threshold if it exceeds a certain degree for a given excitability and then manifests itself by producing a propagated impulse

In order to explain the constant coupling of the extrasystoles the possible importance of the supernormal period of recovery comes first to mind During this phase such sub threshold stimuli of the ectopic centre would temporarily become supra threshold Regard ing the underlying mechanism it was shown that during the supernormal phase the local response to a stimulus of a given strength is larger and turns into a propagated impulse at a lower potential than outside the supernormal period Moreover the propagated impulse

need not arise at the crest of supernormality so that a strict coincidence between coupling and height of super normality need not be postulated Evidence based on the effect of refractory tissue on the local response was also cited which explains that not every beat of the dominant rhythm need be followed by an extrasystole Whether an extrasystole follows each beat of the dominant rhythm or occurs only after a shorter or longer period of un disturbed dominant rhythm is of course only a matter of degree and is likely to depend on quantitative differences in the processes at the centre The inhibiting effect upon the local response of a propagated disturbance and the possible presence of a period of subnormal excitability following the supernormal phase would seem to explain the observa tion that usually only one extrasystole occurs after the initiating beat

The supernormal period is however not the only factor accounting for the occurrence and timing of the extrasystoles It was repeatedly mentioned earlier in this chapter that the activating effect of a propagated impulse could be noted for intervals which were far in excess of the supernormal phase For such instances Hodgkin s observations that the res ponse time rather than the refractory period or the supernormal phase determine the frequency of repetition and that the growth of the local response may be exceedingly slow seem to provide the explanation It seems reasonable to assume that the interval of growth of the local response rather than the supernormal period is the factor determining the length of coupling at least in those instances in which this exceeds the interval during which super normality can be expected to be present The effect upon the local response of supernor mality was discussed above

As far as the processes are concerned which produce the subthreshold background — to borrow a term employed by Erlanger and Gasser (1937)—most of this is still unknown The local changes in potential pre potentials found in various organs to precede the emission of propagated impulses were discussed earlier in this chapter It seems significant that when these were oscillatory in character their damping was found to be smallest in parts of the heart with the greatest automaticity and greatest in those portions which have the least tendency to discharge spontaneously (Bozler) It was also mentioned that various investigators attribute such pre potentials to fluctuations of metabolism a view which is perhaps supported by observations on the relationship between initiation of impulses and O_2 consumption (p 510) Beyond this our ideas are only conjectural In particular it seems obscure whether the underlying stimulus itself is continuous or rhythmical

A wealth of evidence is available to show that continuous stimuli of various kinds and in various circumstances can initiate rhythmical responses If this be the case regarding the ectopic stimulus injury potentials would first come to mind While these seem to be of importance in ectopic beats occurring immediately after myocardial infarction in trauma during cardiac catheterization and possibly certain infections (diphtheria) such explanation is obviously inapplicable to those cases in which occasional extrasystoles with accurate coupling and constant shape are observed over periods of years Since a strictly circum scribed local non progressive abnormality has to be postulated to account for this observa tion such local increase in excitability may *either* be due to some disturbance in the focus resembling in its effect that of sub threshold stimulation in the Wedensky effect or being akin to anodality *or* may be related to the increase in excitability beyond a block that is allied to or identical with the Wedensky facilitation

In the former case local circulatory changes resulting in changes in the ionic milieu would have to be considered in the first instance In the latter case the local abnormality could be imagined to consist of a small permanently altered area partially or completely blocking the spread of the initiating impulse to a small portion of the myocardium and being associated with a temporary increase in excitability beyond the blocked area after each conducted beat

Whether or not a beat initiates an extrasystole in such a focus would depend on the

Of the results of these studies those most relevant to the origin of extrasystoles and of ectopic beats generally may be *summarized* thus

Local changes in potential resulting from metabolic changes apparently being a pre requisite for the discharge of propagated impulses influence upon such local changes of potential of the supernormal phase of a preceding spike independence of response time—corresponding to coupling—from the supernormal phase in the sense that the repetitive responses need not arise at the crest of supernormality and that response time as well as repetition interval may be very much longer than the interval during which supernormality can be assumed to exist influence of the ionic environment on the number of repetition and on the setting up of automatic activity at the site of former stimulation the effect upon the local response of refractory tissue with the result that the particular conditions may lead either to a dying out of the local response or to its growth into another propagated spike the observation that small fluctuations in the strength of a near threshold stimulus may produce very great differences in the local response and excitability with the result that no fundamental difference seems to exist between a wave of activity which just succeeds in propagating and one which just fails the possibility that a higher rate in O_2 consumption is necessary for automatic impulse formation in a centre than is necessary for the conduction of an impulse

MECHANISM OF ORIGIN OF ECTOPIC BEATS

If it is attempted to put forward some views about the mode of origin of ectopic beats on the grounds of the work discussed in this chapter it must be stated at the outset that such views can only be tentative Findings obtained in animal experiments can be applied to human pathology only with great reserve Moreover however great the analogies found between the various excitable tissues here again the greatest caution is necessary in applying findings obtained in one excitable tissue to others All that can be hoped for is to formulate some ideas which based on more recent advances in physiological knowledge and not conflicting with any known facts provide some satisfactory even if only partial under standing of the experimental and clinical observations

For all ectopic beats activity in a circumscribed centre has to be assumed

Extrasystoles

To consider the common variety of extrasystoles with accurate coupling and constant shape first here the activity has to be located in one single circumscribed focus In those numerous instances in which occasional extrasystoles are observed separated by long periods of an undisturbed dominant rhythm the activity in the ectopic centre must be sub threshold for long periods It seems reasonable to assume that it consists of some metabolic change a fluctuation in resting metabolism which as discussed above has also been assumed to underlie the electrical sign of such local processes namely the local graduated non propagated changes in potential Evidence has been discussed which tends to show that such changes consist either in a gradually increasing negativity or in oscilla tions and that increased negativity is associated with increase in excitability Such activity becomes supra threshold if it exceeds a certain degree for a given excitability and then manifests itself by producing a propagated impulse

In order to explain the constant coupling of the extrasystoles the possible importance of the supernormal period of recovery comes first to mind During this phase such sub threshold stimuli of the ectopic centre would temporarily become supra threshold Regard ing the underlying mechanism it was shown that during the supernormal phase the local response to a stimulus of a given strength is larger and turns into a propagated impulse at a lower potential than outside the supernormal period Moreover the propagated impulse

neuromuscular block may be effected the end plate becomes less sensitive to the depolarizing action of acetylcholine or too much acetyl choline is released so that depolarization spreads beyond the end plate region or insufficient amounts of acetyl choline are released by the nerve impulse (Feldberg) Any of those conditions might produce a protective block It would seem a reasonable though admittedly entirely hypothetical assumption to attribute such a protective blocking mechanism to acetylcholine which is known on the one hand to produce block in certain circumstances (for instance decamethonium block Burns Paton and Vianna Dias ganglionic block Paton and Perry) and on the other to initiate ectopic impulses in the heart (discussed in the section on Choline p 328)

Another possibility would be that the conducted S A impulses fail to release a sufficient quantity of acetylcholine at the ectopic centre and thereby the centre is blocked Various conditions are known to produce this effect amongst them calcium deficiency (Brown and Harvey) or perfusion with solutions rich in phosphate (Brown and Vianna Dias) Calcium deficiency is also known to favour automatic impulse formation and in sympathetic ganglia some relationship seems to exist between acetylcholine deficiency failure of transmission of excitation and spontaneous activity in the form of repetitive discharge in the causation of which calcium deficiency appears to play a part (Bronk *et al* 1938 Harvey and McIntosh see also section on Choline) Burn s suggestion (Burn 1950) may be recalled once more in the present context that in cardiac muscle the mechanism for firing off the contraction is also acetylcholine but instead of being liberated by a nervous impulse it is synthetized and causes a contraction probably when a certain concentration is reached It is possible that the pacemaker controls the rate of beating by controlling the rate at which this concentration is reached If it is applicable to ectopic impulse formation it emphasizes the importance of acetylcholine and thus also the conditions which influence its effectiveness That acetylcholine may play a greater part in the conduction of the cardiac impulse than hitherto assumed has been considered by Rothschuh as a result of his findings that the (frog) heart consists electrophysiologically of very small units of the order of 0 1–0 2 m m whereby in the mammalian heart the intercalated discs possibly form the anatomical basis

Since metabolic changes generally are held to underlie impulse formation an explanation along these lines suggests itself

The postulated biochemical disorder in or near the centre would be reminiscent of a similarly localized disorder in myasthenia gravis though this comparison should by no means be taken to imply that identical conditions are assumed

Such a mechanism would also explain at least to a certain extent why automatic impulses do not become manifest during the supernormal phase of beats originating in other centres the altered condition of or near the parasystolic centre namely its reduced excitability as postulated to account for its protection would equally prevent its sub threshold potential changes from becoming supra threshold during the supernormal phase of other beats Only when the automatic impulse has reached a certain intensity in the centre would a propagated disturbance ensue We assume therefore that in parasystole the activity of the ectopic centre is more rhythmical than in extrasystoles and sub threshold processes play a much smaller if any part The mechanism of parasystolic impulse formation would thus be more akin to the normal impulse formation in the S A node

In instances of parasystole with a fast ectopic rhythm the refractoriness produced by the fast ectopic rhythm accounts for the protection of the centre and no further mechanism need be assumed (see chapter on Pararrhythmias)

Relationship between Extrasystolic and Automatic Beats arising in the same Centre

To take these relations in the same order as mentioned above (p 495)

Automatic beats originating in the same focus as extrasystoles Here the extrasystoles

have to be assumed to originate in the way discussed earlier in this chapter In addition there is a periodic protection of the centre caused by the extrasystole in a way unknown which makes possible the undisturbed formation of an impulse in the same centre In addition to the extrasystoles automatic beats are emitted whenever the local potential changes have reached the critical level at which they turn into propagated disturbances This view accords well with some experimental findings on impulse formation in nerve (for instance Arvanitaki Lehmann) and heart muscle (Segers)

Automatic beats followed by extrasystoles originating in the same centre could be understood as an arrhythmia in which the extrasystoles arise in the supernormal phase of the initiating beat in the same centre and in the same way as they are assumed to do after a precipitating beat of the dominant rhythm

The transition from parasystole into an extrasystolic arrhythmia which has been observed on rare occasions is more difficult to explain on the grounds of the observations so far available It could be understood as resulting from the disappearance of those conditions which were discussed as accounting for a protective block of the ectopic centre Such conditions were assumed to be functional ones most probably metabolic in nature (Their functional character would also account for observations of intermittent parasystole and of the disappearance of parasystole after some time which we have not infrequently observed) If owing to metabolic fluctuations the biochemical disorder responsible for the protection of the ectopic focus is no longer present this will be depolarized by the impulses of the dominant centre A condition results in which the sub threshold activities at the centre become supra threshold during the supernormal phase of the preceding beat that is the centre produces extrasystoles with fixed coupling

In conclusion we should like to emphasize once more that the views on the mechanism underlying extrasystolic and automatic impulse formation should only be regarded as working hypotheses Whatever the mechanism is we trust to have adduced adequate reasons for our contention that extrasystolic impulse formation should be separated from the automatic one The former yield propagated impulses *only* during a certain period of enhanced excitability consequent upon an initiating beat in the latter the ectopic impulse formation is independent of such other beat

The first meaning given in the *Oxford Dictionary* for αυτοματος is Self acting having the power of motion or action within itself Clearly no biological phenomenon dependent on another phenomenon of the same kind and initiated by it with a constant time sequence and in a definite though as yet only imperfectly understood manner can thus be called *automatic*

SUMMARY

The thesis is put forward that true *extrasystoles* that is ectopic beats with accurate coupling to the preceding beat (and often with constant shape) in the electrocardiogram are precipitated in the ectopic centre by an initiating beat and are thus a passive derivative phenomenon as distinct from those forms of ectopic arrhythmia in which two (or more) independent automatic centres of equal importance of impulse formation co exist the activity of neither of which is deriving from that of the other For this reason we advocate that true extrasystoles should be separated from automatic ectopic arrhythmias (for instance parasystole)

Alternative hypotheses are discussed which have been put forward to explain extra systoles namely the conception of a parasystolic origin of extrasystoles and that of a circus movement as the underlying mechanism The arguments on which these views are based are discussed and reasons adduced why we consider these hypotheses to be unsatisfactory explanations

The work is reviewed in some detail which demonstrates that extrasystoles arise in one circumscribed focus and that their origin there is dependent on an initiating beat Reasons are given for the statement that the origin of extrasystoles in such a centre is not due to increased automatism of the ectopic focus While the separation between extrasystolic and automatic ectopic impulse formation is stressed it is pointed out that in rare instances the same focus may give rise to extrasystolic *and* automatic ectopic beats

Any views about the physiological processes underlying extrasystolic and automatic impulse formation have to be consistent with the observations that

(1) these two varieties of ectopic beats mostly occur independently from one another and

(2) in some comparatively rare instances these two varieties have been observed to be related to one another in various ways

It is pointed out that our knowledge about this subject is very scanty but that more recent advances in cardiac and nervous physiology have thrown some light on this problem It is emphasized that observations made on one kind of tissue can only with the greatest reserve be applied to another but that analogies in the initiation and conduction of impulses *in living tissue exist which may show the way in which a fuller understanding may be sought*

From this point of view some relevant physiological data about initiation and propagation of excitation are reviewed based on the membrane theory Some re evant work on changes of excitability and of potential after a conducted impulse is discussed It is pointed out that the temporary increase in excitability after a conducted impulse is likely to be of great importance for the occurrence and the timing of extrasystoles This is discussed with special reference to the Wedensky effect the supernormal phase of recovery and allied observations demonstrating an increase in excitability after a propagated disturbance which may last for a considerable time The local graduated non propagated changes in potential at the site of origin of a propagated impulse are described as they were established in nerve and skeletal and cardiac muscle

The repetitive response to a constant stimulus has been observed in various experimental conditions and examples are discussed of this phenomenon resulting from injury electrical and chemical stimulation The bearing which such observations have in emphasizing the role of metabolic factors in the origin of extrasystoles is pointed out

Such observations are considered to support the hypothesis that true extrasystoles arise in a circumscribed focus as the result of sub threshold activity in the ectopic centre temporarily becoming supra threshold during the period of enhanced excitability consequent upon the initiating beat It is pointed out that the supernormal phase while being of paramount importance in the causation of such temporarily increased excitability is not the only factor and that the local potential changes in the centre are likely to exert a profound influence on the time of occurrence of the extrasystole

It is emphasized that whatever the finer mechanism is which produces the extrasystole no circus movement but impulse formation in a circumscribed centre is assumed

Regarding *automatic* impulse formation in particular parasystole it is pointed out that the main difficulty centres around the mechanism of the protection of the ectopic focus against the impulses of the co existent pacemaker The conception of a block zone spherically surrounding the centre while possibly accounting for some instances is unsatisfactory as a general explanation for reasons pointed out in the chapter on pararrhythmias We visualize *such protection as due to reduced excitability of the* ectopic focus The difficulties in reconciling this view with the membrane theory are briefly discussed and it is pointed out by way of a hypothetical assumption that more recent work on acetylcholine seems to indicate that a biochemical disorder may be the underlying condition In cases of parasystole with a fast ectopic rhythm the high rate itself accounts for the protection of the centre and no further mechanism need be assumed

An attempt ıs made at explaınıng those ınstances ın which a relationship between extra systoles and automatic beats has been observed namely automatic beats originating in the same focus as extrasystoles automatic beats followed by extrasystoles arising in the same centre and transition from parasystole into an extrasystolic arrhythmia

In conclusion it is emphasized that our views about the mechanism underlying extra systolic and automatic impulse formation should only be regarded as working hy potheses but that we trust to have adduced cogent reasons for our contention that these two varieties of ectopic arrhythmias should be considered as fundamentally different

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is as in benign gastric ulcer without vagotomy This is given in detail in Section IV If there is failure to respond to medical management or if malignancy should be suspected at any time surgical intervention obviously is indicated

Perforation Hemorrhage and Obstruction These are treated as when occurring without vagotomy Details of treatment of these complications are discussed elsewhere (Chapters 60 61 63 and 64)

For discussion of the present status of vagotomy see Chapter 50

MEDICAL MANAGEMENT AFTER GASTRO ENTEROSTOMY AND PARTIAL AND SUBTOTAL GASTRECTOMY WITH AND WITHOUT VAGOTOMY

The problems in medical management after partial and subtotal gastrectomy and gastro enterostomy either with or without vagus resection are for the most part similar Differences as will be seen are chiefly in degree and in frequency

The more prominent organic conditions common to both are (1) anastomotic ulcer with its complications the latter being hemorrhage perforation with or without gastrojejunocolic fistula and obstruction and (2) postoperative gastritis and jejunitis

The primary functional problems in both are known as the "dumping syndrome and the 'hypoglycemic syndrome Together they are also designated as the postgastrectomy syndrome In addition there are certain similar metabolic and nutritional disorders seen with both states

For a discussion on the present status of gastro enterostomy and partial as well as subtotal gastric resection see Chapters 48 and 49 respectively

The Anastomotic Ulcer

Ulcer or ulcer like symptoms arising at any time after a gastrojejunal anastomosis for relief of duodenal ulcer particularly when associated with free hydrochloric acid with or without vagus resection should arouse the suspicion of the presence of an anastomotic ulcer

Prophylaxis The anastomotic ulcer can sometimes be prevented if indications for surgery are held strictly and rigidly the proper operation performed when the procedure becomes necessary and active protracted medical management followed The last mentioned should include a continuation of between meal feedings and between meal nonadsorbable antacids elimination of coffee tobacco and alcohol because of their acid stimulating properties as well as avoidance of tensions and anxieties

Therapy The reader is referred to Chapter 54 for a discussion of therapy Briefly this may be summarized as follows The patient should be hospitalized and the most rigid medical regimen instituted (see Chapters 29 through 36) When necessary the continuous nasogastric drip of Winkelstein [9] might be used Not infrequently the anastomotic ulcer like gastric and duodenal ulcer runs a mild course and even heals spontaneously However the tendency of the lesion to hemorrhage penetration perforation and refractoriness to treatment is well known and these frequently justify surgical intervention If the stomal ulcer followed a gastro enterostomy a

subtotal gastrectomy might be performed except when the condition of the patient or technical difficulties make this unfeasible then a vagotomy will be in order (see also Chap 48) If the stomal ulcer occurred after an adequate subtotal gastrectomy vagotomy will be warranted to control the neural phase of gastric secretion [3] [7] the gastric phase having been curtailed to some degree by the original operation

Complications of Anastomotic Ulcer ACUTE PERFORATION should be suspected when signs of an acute abdomen" are present in a patient who has had an anastomotic operation Induration or a mass in the region of the stoma should suggest a *chronic walled off perforation* In both instances operation is indicated (See also Chapter 54)

GASTROJEJUNOCOLIC FISTULA. See Chapter 57

Gastritis and Jejunitis

Varying degrees of gastritis and to a lesser extent jejunitis occur in many patients with subtotal gastrectomy [19] This is much less so with gastroenterostomy [19] Vagotomy does not protect from these changes [1] Gastritis jejunitis and acute erosions of the stomach and contiguous jejunum may account for bleeding at times However there are some who find it often difficult to correlate other upper digestive tract symptoms with these alterations [15] These changes discernible by gastroscopy may be approached as follows in a general way the gastritis and jejunitis are to be treated essentially as an uncomplicated duodenal ulcer and bleeding is to be managed as is bleeding from a duodenal ulcer When hemorrhage is not a factor in the writer s experience treating the patient primarily results in greater progress than in principally treating the local process

The Medical Management of the "Dumping" and "Hypoglycemic" Syndrome "Postgastrectomy State"

The symptoms of "dumping" and "hypoglycemia" are similar their temporal relationships to food intake and pathogenesis are different [2] [13] In "dumping" upper abdominal fulless and discomfort palpitation or pounding of the heart anxiety weakness sleepfulness nausea with or without vomiting occasional sweating and light headedness sometimes prostration and a sense of impending syncope come on during or within a half hour after eating In the hypoglycemic state similar symptoms appear two to four hours after eating In the dumping syndrome jejunal distention occurs either because of rapid gastric emptying or the taking of hypertonic solutions which increase the volume of the jejunal juices through changes in osmotic pressure which in turn distends the jejunum and accounts for the difficulty In the hypoglycemic syndrome the symptoms obviously are associated with marked lowering of the blood sugar due to too rapid absorption of sugar In both conditions tensions and anxieties exaggerate symptomatology Other manifestations associated with either condition are not characteristic Some of these are wasting deficiencies in vitamins organic and inorganic constituents and hematologic changes Both conditions taken together have been designated as the "postgastrectomy state" The diagnosis will be readily made by thinking of these possibilities after a gastrojejunostomy with or without vagotomy

Therapy This is simple if the condition is diagnosed The dietetic principle in both the dumping syndrome and hypoglycemia consists of frequent, small dry feedings relatively high in protein, fluids, taken slowly are not to be given at mealtime This routine tends to reduce the rushing of food into the upper small intestine diminishes the taking of hypertonic solutions and tends to stabilize highly fluctuating blood sugar levels [6] thus eliminating the more readily absorbable sugars

Other nonspecific manifestations accompanying this syndrome to which reference has been made are to be treated accordingly when present (replacement therapy) Some add liver extract apparently empirically

The success of the foregoing measures in either or both of the foregoing syndromes often bears a direct relationship to the thoroughness in managing the patient from the standpoint of the whole as well as his family

UNINTENTIONAL GASTRO ILEOSTOMY

Unintentional gastro ileostomy is performed erroneously for a gastrojejunostomy on rare occasions (see Chap 56) The clinical picture is similar to that occurring in gastrojejunocolic fistula (see Chap 57) The management preliminary to life saving surgical correction is essentially that used in gastrojeunocolic fistula Two such cases have come to the writer s attention in recent years (For detailed discussion on diagnosis and treatment of gastro ileal ulcer see Chapter 56)

MEDICAL MANAGEMENT AFTER TOTAL GASTRECTOMY

Total gastrectomy when done is usually for the extirpation of gastric carcinoma On rare occasions the necessity of the removal of an inaccessible gastric ulcer, sometimes multiple ulcers or complications in the face of a subtotal gastrectomy makes this operation unavoidable The procedure is usually an esophagojejunostomy sometimes when it is technically possible it is an esophagoduodenostomy

There are few available data bearing directly on the subject of the medical management of total gastrectomy The observations and interpretations are based on the writer s study[16] in the past six years of fifty such cases of more than eighty performed at The Johns Hopkins Hospital for carcinoma among which were three for benign gastric ulcer Except for the problem of recurrence of malignancy and metastases the considerations in medical management seem to be essentially the same regardless of the nature of the lesion for which the operation is performed

In the absence of the stomach there are five factors in need of medical management (1) the mechanical (2) the functional (3) the metabolic and nutritional (4) inflammatory changes and (5) hematologic alterations

1 *Mechanical difficulties* arise from the small capacity and lack of ready distensibility of the esophagus and contiguous jejunum or duodenum This results in chest oppression and upper abdominal fullness when eating relatively normal quantities based on usual habits in the face of a fair to good appetite It is more difficult to handle fluids particularly when taken quickly especially water and carbonated beverages There is regurgitation

of intestinal juices called "spitting up" by the patient which may be due at least partly to the loss of the cardiac and pyloric sphincters

These are relieved to varying extent by the omission of liquids with meals six feedings of a bland diet of concentrated foods relatively high in protein and offering a minimum of mechanical chemical and thermal stimulation Fluids are taken slowly and in smaller quantity during the other periods of the day As months pass alterations can be made since the symptoms become less pronounced as the upper jejunum dilates somewhat and the patient learns to live without his stomach and accept its limitations Urecholine to ameliorate "spitting up" will be discussed shortly

2 The *functional problems* are those of "dumping"[13] and hypoglycemia also known together as the "postgastrectomy" state They are often of a more marked degree than in gastro-enterostomy and partial gastrectomy The absence of any stomach accounts for this The management here is identical with that previously referred to in this chapter as occurring with partial or subtotal gastrectomy or gastro enterostomy

3 *Metabolic and Nutritional Factors* Protein and inorganic elements appear to be metabolized satisfactorily but not so with carbohydrates As much as 35 per cent[11, 24] of the daily ingested fat is excreted in the feces Yet the small intestine motility and mucosal pattern radiologically are usually essentially normal There are two to three well formed stools daily The lack of adequate fat absorption probably accounts for the inability of patients to regain optimum weight Detergents have not been helpful Some patients after hospital discharge show a slight reduction in serum albumin probably due to insufficient protein intake This should be watched for There should be insistence on greater protein ingestion or if necessary the daily addition of protein hydrolysates should be prescribed

4 The *inflammatory changes* are those of a low grade distal esophagitis and jejunitis sometimes intermittent and of varying degrees of severity The jejunitis has apparently been observed for the first time through the gastroscope by this writer[16] These changes may account for upper abdominal and substernal burning Regurgitation of intestinal juices may play a role in this symptom The treatment is not wholly satisfactory adsorbents sedatives and urecholine have been used The last mentioned is given in 5 to 10 mg doses three times a day before meals Hydrochloric acid and glutamic acid hydrochloride have not been helpful

5 *Hematologic Alterations* The stomach is essential in hematopoiesis In some patients with total gastrectomy an iron deficiency anemia develops rather early Therefore ferrous gluconate 0 3 gm three times a day after meals on alternate weeks will prevent this However other forms of anemia tend to manifest themselves for which there is no specific therapy save that for pernicious anemia which often develops if the patient lives long enough[27]

SUMMARY

The etiology of peptic ulcer is not settled The so called psychosomatic theory is attractive but multiple factors are probably involved Nonetheless from the point of view of *treatment* experience in a general way indicates that managing the patient not solely but primarily from the

standpoint of the whole is often more effective than principal regard for the functional derangement or local lesion without stress on personality Thus emphasis has been placed on managing the patient who has had operation for peptic ulcer from this psychobiologic point of view Methods of approach and simple technics have been outlined

Since prophylaxis is the ultimate desideratum in therapy mention has been made of the necessity of properly interpreting symptoms and signs to avoid unnecessary operation

The organic and functional deviations which follow the operations commonly performed for the relief of peptic ulcer its sequelae and complications have been pointed out and therapeutic procedures outlined

For accuracy in diagnosis and treatment attention has been directed to the several conditions distress from which at times may simulate disturbances of the upper digestive tract after operation for ulcer

The dietotherapeutic and pharmacotherapeutic principles after the several operations for relief of peptic ulcer are simple and few The diet is of reduced physical chemical and thermal stimulation to facilitate reduction in local irritability thus allaying distress Frequency of feedings is to avoid load or to help dilute if not adsorb acid Antispasmodic and anticholinergic drugs are used to depress the vagus nerve which in turn results in depressing digestive tract tone and gastric secretion to varying degrees cholinergic drugs are given in vagotomy to stimulate vagal nerve endings when necessary and sedatives and hypnotics are prescribed to influence the central nervous system and possibly in part the psyche

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Chapter 48

PRESENT STATUS OF GASTRO ENTEROSTOMY FOR PEPTIC ULCER

WALTMAN WALTERS

Although gastro enterostomy has been followed by satisfactory results in selected cases in my experience the preferable operation for patients with chronic recurring duodenal ulcer especially if perforative or hemorrhagic complications have been present has been partial gastrectomy with removal of two thirds of the stomach and a Polya type of anastomosis

The frequency with which various operations have been performed in the treatment of chronic recurring duodenal ulcer at the Mayo Clinic from 1935 through 1949 is shown in Figure 112 The trend toward a greater number of gastric resections and a decreasing number of gastro enterostomies is evident and significant Yet reference to Table 35 in which the number of cases in which vagotomy was performed with and without other operations on the stomach and the number of cases in which gastro enter

ostomy was performed shows that in 1949 the decrease in the number of gastro enterostomies alone to fifty two is made up for by the number (40) of patients who had gastro enterostomy with associated vagotomy The total is practically the same as the total number of gastro enterostomies

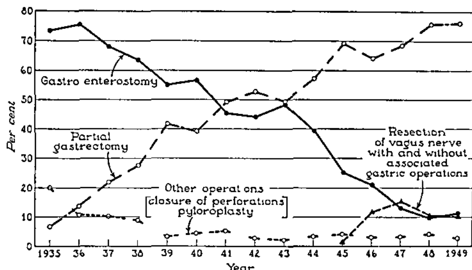


Fig 112 Operations for duodenal ulcer performed at the Mayo Clinic from 1935 through 1949

(90) performed for duodenal ulcer in 1945 It is interesting to note that only two of the forty seven patients on whom vagotomy was performed for duodenal ulcer in 1949 had vagotomy without some additional drainage

Table 35 Duodenal Ulcer

OPERATION	1945	1946	1947	1948	1949
Partial gastrectomy	247	296	317	325	355
Gastro enterostomy only	90	82	55	42	52
Vagotomy only	2	14	16	3	2
Vagotomy and gastro enterostomy	2	28	42	36	40
Vagotomy and gastro duodenostomy	1	4	6	0	1
Vagotomy and partial gastrectomy	0	0	1	6	4

operation on the stomach indeed forty of the forty seven patients were treated by gastro enterostomy combined with the vagotomy

FUNCTION OF GASTRO ENTEROSTOMY

One of the most important functions of gastro enterostomy is to relieve gastric and duodenal obstruction This allows the stomach to empty more rapidly in the presence of a recurring duodenal ulcer When a duodenal ulcer is present, the stomach is prevented from emptying rapidly by ob

struction due to the fibrosis and edema or pyloric and duodenal spasm Another important effect of gastro enterostomy is that it reduces gastric acidity This is accomplished by reflux of alkaline duodenal biliary and pancreatic secretions into the stomach through the gastro enteric stoma This reflux lessens the irritation of the duodenal ulcer by the hydrochloric acid as a consequence gastric spasm is reduced Should this reflux of alkaline secretions into the stomach be prevented by an enteroanastomosis between the loops of jejunum from which the gastro enteric anastomosis is made little if any reduction of gastric acidity occurs and there is a high incidence of ulceration at the gastrojejunal stoma

VARIATION IN BEHAVIOR OF LESIONS

It is important in surveying the results of the use of any form of treatment for any surgical lesion to have a full understanding, first of the pathologic lesion and its variations in different races sexes and age groups for which the operation is performed as well as the variations in the response of patients in these groups to the same surgical procedures

Some of the differences in the benign gastric inflammatory lesions associated with duodenal ulcer should be mentioned In 1931 Snell and I[12] pointed out that whereas in the United States the incidence of gastric ulcer associated with duodenal ulcer was about 1 to 10 in Germany the incidence was 1 to 2 or 1 to 3 and that 90 per cent of the German patients who had resections for chronic duodenal ulcer had various demonstrable degrees of gross gastritis frequently ulcerating in type Such associated gastric lesions are infrequently seen in patients who have duodenal ulcer in the United States It is evident therefore that for ulcerating duodenal and gastric lesions the problem of treatment in these two countries is different Schittenhelm[7] called attention to this geographic variation in disease Certainly it would be to the advantage of the patient with associated ulcerating gastric lesions to have the area of ulceration not only of the duodenum but also of the stomach removed

There is a striking racial difference also in the response to the effects of gastro enterostomy in the treatment of chronic duodenal ulcer The incidence of recurring ulceration is much higher among Jewish patients after gastro enterostomy and indeed after partial gastrectomy as well than among gentiles It has been almost universally recognized for a long time that surgical treatment of duodenal ulcer of patients in the younger age groups has given less satisfactory results than on patients in the middle or older age groups Women have duodenal ulcers less frequently than men but their response to any type of surgical procedure for it including gastro enterostomy is usually followed by excellent results Few women have gastrojejunal ulcers after a properly performed gastro enterostomy These factors play an important role in a study of any type of surgical treatment of duodenal ulcer and must be taken into account in the evaluation of the effects of gastro enterostomy

GASTRO ENTEROSTOMY OR SOME OTHER PROCEDURE FOR RECURRING DUODENAL ULCER

Favorable Results of Gastro enterostomy I have not seen any better results from any surgical procedure or any more satisfied patients than

those patients who have had a properly performed gastro enterostomy for chronic recurring duodenal ulcer whose stoma is functioning satisfactorily and who have had no indication of gastrojejunal or jejunal ulceration Because of the satisfied patients and the fact that at the Mayo Clinic there was a relatively low incidence of proved recurring ulceration when gastro enterostomy had been done for the treatment of the selected patient with chronic recurring duodenal ulcer the operation has continued to be used Results have been excellent in most cases

Numerous reports support this statement For example in 1928 a collective investigation into the course after gastro enterostomy was carried out by the British Medical Association Patients operated on in various parts of the British Empire during the period 1920 to 1924 inclusive[4] were considered This report stated Secondary gastrojejunal ulcer occurred in 2 8 per cent of 744 cases in which gastro enterostomy was performed for duodenal ulcer The results of the operation were satisfactory in about 90 per cent of the cases

Eusterman and Balfour[1] in 1935 commented as follows "In a series of 500 consecutive cases of duodenal ulcer studied in which gastro enterostomy only was performed the results were computed on the basis of reports received from patients a minimum of five years after operation There were 416 males and 84 females a ratio of 5 1 A survey of these reports revealed that 87 per cent of the patients had experienced relief of symptoms"

In another study these same authors reported the results of gastro enterostomy on 100 physicians They summarized as follows Complete relief of symptoms was reported in 87 per cent of the cases in which posterior gastro enterostomy was performed The average time since operation in this group was eight and a half years There were six cases (6 7 per cent) in which symptoms recurred to some extent but such symptoms were either corrected by subsequent operation or were controlled by care in diet Five cases in this group were considered as failures in four of which symptoms were due to recurring ulceration and in one to disease of the gallbladder"

It is interesting that in the series of seventy seven patients on whom I performed vagotomy for various types of peptic ulceration up to January 1949 excellent results followed the performance of gastro enterostomy and vagotomy for duodenal ulcer in 87 per cent of the patients so treated This figure it will be noted is identical with that reported by Eusterman and Balfour for the 100 physicians who had a posterior gastro enterostomy *without* vagotomy

The safety of gastro enterostomy was emphasized by Moynihan[5] who stated In my last 1000 cases of operation for duodenal ulcer I have had one death" I doubt whether this record has been equaled by anyone else but certain it is that gastro enterostomy when performed for chronic recurring duodenal ulcer by a surgeon of experience on a patient who has had adequate preparation before operation and who has adequate postoperative care should not carry a risk of more than 1 per cent Eusterman and Balfour[1] in 1935 quoted Gaither as follows "In view of the low immediate mortality and splendid end results after gastro enterostomy there is no justification for displacing them for subtotal gastrectomy with its higher immediate mortality rate"

Present Operation of Choice This was written in 1933 but I am sure that Gaither s opinion my opinion[10] and that of other American surgeons has shifted in recent years in favor of the more radical procedure of partial gastrectomy The reason for this shift is that partial gastrectomy not only accomplishes everything that posterior gastro enterostomy does but does it better It reduces the amount of gastric secretion produces a more complete reduction of hydrochloric acid to a relative achlorhydria, and the mortality rate compares favorably with that of gastro enterostomy * In these circumstances gastro enterostomy would be chosen only because of its lower risk for patients with large perforating obstructing duodenal ulcers in which the risk of the removal of the ulcer or of leaving it in the performance of a partial gastrectomy greatly exceeds that of the same operation when the duodenal ulcer can be easily mobilized and removed and accurate and safe closure of the duodenum accomplished

In addition to these important and valuable benefits of partial gastrectomy over gastro enterostomy there is a definite decrease in the incidence of gastrojejunal ulcer following adequate partial gastrectomy over that following gastro-enterostomy Starlinger[8] summarized 26 000 cases in which adequate partial gastrectomy had been performed for duodenal ulcer in the Central European clinics There was recurring ulceration in 2 5 per cent In several series of cases published from the various clinics in the United States the incidence of recurring ulcer following a properly performed adequate partial gastrectomy for chronic recurring duodenal ulcer usually has been about the same (2 per cent) There seems to be constant agreement about this figure

Opinions differ widely regarding the incidence of recurring ulceration after gastro enterostomy and the somewhat high incidence in some series is responsible for the objection to this procedure in the treatment of duodenal ulcer I have quoted from the statistics of the British Medical Association on the incidence of recurring ulceration after gastro enterostomy an incidence similar to our experience at the Mayo Clinic In several series of cases studied by Eusterman and Balfour the incidence of recurring ulceration was about 3 5 per cent On the other hand Gaither (*see* Chap 54) quotes Lahey as saying that in the latter s experience the incidence of recurrent ulceration after gastro enterostomy was 15 per cent In the series reported by Lewisohn in the 1920 s the proved incidence of recurring ulceration in patients mostly Jewish operated on at Mount Sinai Hospital was 16 per cent while an additional 16 per cent of patients were suspected of having recurring ulceration In the first group the recurring ulceration was proved at roentgenologic examination and by reoperation Such methods of confirming the clinical diagnosis were not available for the 16 per cent suspected of having a recurrence Lorenz and Schur [3] in their pioneer work on the application of partial gastrectomy for duodenal ulcer reported that the maximal incidence of recurring ulceration after gastro enterostomy for duodenal ulcer was 10 per cent Vanzant and associates stated that their follow up studies failed to show that one can predict from the acidity which patients will have a jejunal ulcer and which will not

Gaither in Chapter 54 states "A circumspect review of the literature invariably leads to the conclusion that no individual estimate of the inci

* Unfortunately it does so with the loss of a considerable portion of the stomach which cannot be replaced This is not the case when a gastro enterostomy is performed

dence of jejunal and gastrojejunal ulcer is entirely reliable and no two estimates are strictly comparable" With this I heartily agree

On the other hand, Gaither wrote "The millenium with regard to the elimination of gastrojejunal ulcer promised by those who pioneered in the operation of subtotal gastric resection in the treatment of peptic ulcer has not come It is now known from bitter experience that this complication does occur in all too many cases in which the gastric mucosa is anastomosed to the small intestinal mucosa whether it be by gastro enterostomy some other conservative procedure or a more radical operation such as subtotal resection of the stomach" For this reason the search has continued for better surgical methods to improve the results and reduce the incidence of recurring ulceration

Procedures Combined with Gastro enterostomy This is not the place to contrast other surgical methods of treating duodenal ulcer except as they apply to a procedure which might be done in association with gastro enterostomy Such a procedure should increase the reduction in the quantity of gastric secretion lower the concentration of free hydrochloric acid in the gastric secretion and decrease the incidence of recurring gastrojejunal ulceration I refer to the operation of vagotomy which now is being combined with gastro enterostomy by some surgeons who use gastro enterostomy as a surgical method for the treatment of duodenal ulcer

A gastro enterostomy added to vagotomy in the treatment of duodenal ulcer prevents the retention and accumulation of gastric secretions within the stomach which is troublesome to the patient But it must be remembered that the same degree of reflux of alkaline duodenal biliary and pancreatic secretions into the stomach occurs as though the vagotomy had not been done with the gastro enterostomy I believe that this after effect is the reason for most of the beneficial results of the combined operation Comparison of the results of vagotomy without gastro enterostomy with those of vagotomy and gastro enterostomy in my experience shows excellent results in 57 per cent of the former group and in 87 per cent of the latter It is evident therefore that gastro enterostomy either with or without vagotomy is a valuable procedure in selected cases

Factors in the Selection of the Operation The decision concerning what operation should be done for various patients rests largely on the experience of the surgeon and his results with gastro enterostomy and other types of gastric and duodenal surgical procedures particularly partial gastrectomy with removal of the duodenal ulcer In most surgical clinics and indeed those hospitals in which many surgeons are doing gastric surgery the risk of partial gastrectomy for duodenal ulcer rests largely on the skill and experience of the surgeon If he can perform partial gastrectomy and partial duodenectomy with removal of the duodenal ulcer in such a way that leakage will not occur from the closed end of the duodenum the risk is relatively low This procedure necessitates in many cases meticulous dissection and removal of a large frequently perforated duodenal ulcer from the pancreas After this dissection sufficient duodenum should remain so that it can be accurately closed without fear of leakage If the ulcer is low in the duodenum rather than risk interference with the motility of the ampullary portion of the common bile duct through the papilla of Vater the surgeon may think it best to leave the duodenal ulcer but always resect the stomach to below the pylorus

Some surgeons have felt that in their hands partial gastrectomy and partial duodenectomy with removal of a large duodenal ulcer carries a prohibitive risk therefore some of them who have continued to use gastro-enterostomy have begun to combine it with vagotomy in certain cases It remains to be seen whether or not the addition of vagotomy to gastro-enterostomy will improve the results of gastro-enterostomy and decrease the risk of recurring ulceration Sufficient time has not elapsed for this problem to be determined for as Priestley and Gibson[6] showed, recurring ulceration does not manifest itself for an average of three and a half years after gastro-enterostomy Since many patients who have undergone gastro-enterostomy do not have evidence of recurring ulceration until many years after the operation sufficient time will have to elapse to determine whether or not the vagotomy has given additional benefit (see Chap 50)

In my experience when gastro-enterostomy has been done in preference to partial gastrectomy for those patients whose acids were high, who had a large perforating duodenal ulcer and who were in the middle decades of life it has been worth while to add a vagotomy in certain selected cases

Gastro enterostomy without vagotomy is most likely to be indicated, it seems to me for the elderly patient who has a high degree of gastric obstruction which has taken its toll on the nutritional state of the patient and who has a serious disturbance of salt water and nitrogen metabolism and avitaminosis Many of these patients in spite of an adequate period of preparation and compensation for the dehydration and their poor nutritional state are in poor condition for any major surgical procedure Gastro-enterostomy can be done on such patients at a comparatively low risk with life saving results Abdominal wall block with a local anesthetic agent supplemented by a small amount of gas is the anesthesia of choice The benefit of such a procedure by the improvement of the patients general health and nutritional state is one of the most astonishing accomplishments in surgical therapy Other patients too less sorely depleted of fluids salt and vitamins whose nutritional state is not so bad and who have chronic ulcer with low gastric acids easily do well with gastro-enterostomy The same applies to middle-aged or elderly women although for the former group I prefer partial gastrectomy if it can be done with equal safety to gastro-enterostomy

GASTRO-ENTEROSTOMY AND OTHER PROCEDURES FOR GASTRIC ULCER OR GASTROJEJUNAL ULCER

Two decades ago the surgical excision of a gastric ulcer with gastro-enterostomy was not infrequently performed especially on patients with high gastric lesions This procedure was followed in most cases by excellent results because practically all the patients obtained a relative achlorhydria from the operation and recurring ulceration was infrequent. With the improvements in surgical technic as a result of experience however it has become more and more evident that partial gastrectomy is the preferable procedure in the treatment of all ulcerating gastric lesions since with surgical experience the risk is no higher usually than for excision of the ulcer and posterior gastro-enterostomy and the results I believe are superior

In the presence of gastrojejunal ulceration following gastro-enterostomy in my opinion there is no place for a second gastro-enterostomy or excision

of the gastrojejunal ulcer and reconstruction of the gastro enteric stoma unless vagotomy is done in association Without vagotomy the patient is almost certain to have another recurring gastrojejunal ulcer whereas if complete vagotomy is done and achlorhydria is obtained excellent results have followed in 87 per cent of the cases[6] in which the gastro enteric anastomosis is allowed to remain over the short period that the patients have been followed that is in a matter of a few years The preferable procedure in such circumstances however in my experience is the removal of the gastro enteric anastomosis and adequate partial gastrectomy[11]

TECHNICAL ASPECTS OF GASTRO ENTEROSTOMY

Although space does not permit a discussion of the details of surgical technic which we have followed at the clinic in the performance of gastro enterostomy certain statements should be made The preferable anastomosis I believe is made by attaching a loop of jejunum to the posterior wall of the stomach posterior to the colon The site of anastomosis on the loop of jejunum is approximately 3 or 4 inches (7 6 to 10 2 cm) from the ligament of Treitz and the gastrojejunal stoma is approximately 4 to 5 cm in diameter The opening in the stomach should be so placed that it lies diagonally across the dependent part of the stomach neither too high nor too low usually opposite the esophagus At the clinic we have followed the plan of making the opening of the stomach a diagonal one extending from a point midway between the greater and lesser curvatures to a point at the greater curvature The proximal part of the jejunum is attached to the former and the distal part of the jejunum to the latter The opening made in the transverse mesocolon to permit this anastomosis should be closed by suturing its edges to the stomach slightly above the point of the gastrojejunal anastomosis When gastro enterostomy is done for the treatment of duodenal ulcer an enteroanastomosis should never be done because as previously mentioned gastric acidity is reduced only infrequently after this procedure and the incidence of recurring ulceration is high

When the transverse colon is so short that an adequate opening cannot be made in the avascular area of the transverse mesocolon between the arcades of the middle colic blood vessels the anastomosis is made anterior to the colon and on the anterior wall of the stomach Again the site chosen is the dependent part of the stomach opposite the esophagus but the anastomotic opening is a longitudinal one just above but following the greater curvature of the stomach A loop of jejunum of sufficient length is chosen that may be brought up around the transverse colon and the greater omentum (gastrocolic) and attached to the anterior wall of the stomach without tension This length of jejunum varies and is dependent on the size of the patient and the amount of fat in the gastrocolic omentum Usually it is about 14 inches (35 6 cm) from the ligament of Treitz I prefer to have the distal part of the jejunum toward the pylorus

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Chapter 49

PRESENT STATUS OF SUBTOTAL GASTRIC RESECTION

ALBERT M SNELL

Partial gastric resection is generally regarded as the procedure of choice in dealing with complicated or intractable peptic ulcers As Lake[17] has said of the operation it is the only method of treatment of ulcer which has steadily and consistently increased in popularity It did not reach this position of eminence by a quick or easy route As a previous chapter indicates gastric resection supplanted the previously advocated operation of gastro-enterostomy only after a long and at times a bitter controversy (see Chap 40)

The tendency in most clinics throughout the world today is clearly defined Medical treatment is recommended for the large majority of ulcer patients while a diminishing percentage of cases (10 to 15 per cent of the total) is subjected to an operation which has been demonstrated by experimental studies to reduce the gastric secretion of hydrochloric acid (see Chap 43) and to provide a maximum degree of protection against recurrent ulceration (see Fig 112 p 522) It is the purpose of this chapter to survey the results of the operation as recorded in the literature So general has been the acceptance of partial gastrectomy as the favored method of dealing with ulcer that many have been inclined to inquire as Allen and Welch[3] have recently done whether "we may have deluded ourselves regarding this procedure"

It should be stated at this point that this chapter is prepared in advance of an extensive survey on the results of partial gastrectomy which is being carried out by the National Committee on Peptic Ulcer with the aid of funds provided by the United States Public Health Service (see Chap 50) Until this survey is completed a matter which may require some years all

statistics on the results of the operation should probably be weighed and compared with a certain amount of caution The reasons are apparent to everyone who may have attempted a similar task The available statistics come from large institutions and teaching centers they do not necessarily apply to smaller hospitals and less experienced surgeons There is no unanimity of opinion as to what constitutes a "satisfactory" a fair or an unsatisfactory" result Rates of recurrence are also of little value unless one knows whether the author refers only to recurrences surgically verified or includes those cases showing roentgen evidence of recurrence plus those which may have suffered from late postoperative hemorrhage Finally as many critics have pointed out the method of follow up by letter and questionnaire is open to grave objection one cannot assume that data on the outcome in the major part of a group of patients operated upon necessarily would be duplicated in the minority group which have not been traced

An even more knotty problem remains to be considered in evaluating end results Was the resection adequate according to the criteria set forth by Wangensteen in Chapter 43? It is notoriously difficult to be certain how much of the stomach is removed at operation and surgical notes are often misleading in this respect As Ogilvie [9] states some resections are little more than ceremonial circumcisions of the stomach Apparently too the length of the jejunal loop and its position in respect to the colon are of some importance in the end result Finally one should know accurately what disposition was made of the ulcer itself and the mucosa of the pyloric antrum since retention of antral mucosa appears to defeat the purpose of the operation The whole matter has been neatly summarized by Mage [1] who wrote "The statistical confusion which exists concerning the effects of various treatments for peptic ulcer cannot be settled until some generally accepted logical method is devised for studying results in a uniform way and with a particular provision for the manifold variables which make for unwarranted actual and comparative inferences"

In the tables and discussion to follow the writer has attempted to utilize recent statistical reports from leading hospitals and teaching centers in which the length of the follow up study and the percentage of cases traced seemed satisfactory There are of course wide variations in the surgical procedures in the various series reported ranging from the radical type of resection recommended by Visick[14] to the relatively conservative operation done by Rienhoff[34] and others A more detailed analysis of the end results in respect to the various types of resection must await the report of the National Committee on Peptic Ulcer

IMMEDIATE AND REMOTE RESULTS OF PARTIAL GASTRECTOMY

Experimental physiologists have demonstrated repeatedly over a period of about seventy five years that animals can do well with only a remnant of a stomach or indeed with no stomach at all The earlier animal and human studies cited by Gordon Taylor and his associates [10] make interesting reading today General clinical experience with the partially gastrectomized human has recently been well summarized by Ingelfinger [14] He points out that while there are numerous variables introduced by the extent of the resection and the temperament of the patient certain facts regarding the general physiologic effects of partial gastrectomy can be regarded as established These may be enumerated as follows

1 *Effects of Nutrition* A certain percentage of patients do not regain their normal or even their preoperative weight The figure usually given is 30 per cent which seems rather high although Gaviser's[9] carefully compiled figures are in agreement There is good evidence to indicate that after partial gastrectomy carbohydrates and proteins are adequately absorbed so that one cannot explain weight losses on this basis The rapidity of glucose absorption is shown by the rapid development of an alimentary hyperglycemia in these patients this in turn may be followed by a definitely hypoglycemic phase coming some three hours after the ingestion of glucose Fat absorption is impaired probably in proportion to the size of the gastric resection There are relatively large losses in the totally gastrectomized patient and appreciable amounts may be lost after partial gastrectomy as Wollaeger and his associates[50] have shown by carefully conducted metabolic experiments

In view of what has been said about the absorptive capacity of the resected stomach it is interesting to note the patients reported by McDuff and Morlock[23] who had had gastric resections in youth and who were observed twenty one and thirty five years later One had developed normally but the other had had some difficulty in maintaining weight

2 *Effects on Gastric Motor Function* About 10 per cent of patients suffer some mild or moderate postcibal distress presumably due to their small gastric capacity A few have loose stools shortly after eating this may be related to rapid gastric emptying which is usually present The gastric remnant as shown by serial roentgenologic studies gradually enlarges and resumes some of its functions as a food reservoir There may be and often is some associated distention of the upper jejunum The symptoms usually subside with this compensatory dilatation of the stomach and bowel There may however be persistent motor difficulties for long periods postoperatively some of which are probably due to organic difficulties while others are on a purely functional basis

3 *Effects on Gastric Secretion* The degree to which the secretion of hydrochloric acid is depressed by partial gastrectomy has been the subject of many studies and there is a wide range of variation in observed results It seems well established that small amounts of free acid can almost always be obtained after histamine stimulation especially if the patient is placed in a position to permit optimum collections of secretion from the small hypermotile gastric remnant With routine test meals however complete anacidity is reported in a high percentage of cases Gaviser[9] and Watson[49] put the figure at about 85 per cent or better Walters estimates that at least 60 to 75 per cent of patients have a permanent anacidity while a majority of other authors report figures between these two points

There is an observed difference between the acid responses of patients with gastric and duodenal ulcers after resection a far larger percentage of gastric ulcer patients show a postresection anacidity Patients with anastomotic ulcers after gastro enterostomy fall into still a different category they are likely to have a persistent hypersecretion of free hydrochloric acid before and frequently after adequate resection

4 *Effects on Blood Formation* Anemia after gastric resection has received much attention because of the possible loss of intrinsic hematopoietic factor after this operation However pernicious anemia seems to be an extremely uncommon development even normochromic or hypochromic anemias of moderate degree are only infrequently encountered.

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In the tables and discussion to follow the writer has attempted to utilize recent statistical reports from leading hospitals and teaching centers in which the length of the follow up study and the percentage of cases traced seemed satisfactory There are of course wide variations in the surgical procedures in the various series reported ranging from the radical type of resection recommended by Visick[44] to the relatively conservative operation done by Rienhoff[34] and others A more detailed analysis of the end results in respect to the various types of resection must await the report of the National Committee on Peptic Ulcer

IMMEDIATE AND REMOTE RESULTS OF PARTIAL GASTRECTOMY

Experimental physiologists have demonstrated repeatedly over a period of about seventy five years that animals can do well with only a remnant of a stomach or indeed with no stomach at all The earlier animal and human studies cited by Gordon Taylor and his associates [10] make interesting reading today General clinical experience with the partially gastrectomized human has recently been well summarized by Ingelfinger [14] He points out that while there are numerous variables introduced by the extent of the resection and the temperament of the patient, certain facts regarding the general physiologic effects of partial gastrectomy can be regarded as established These may be enumerated as follows

Table 36 Results in Per Cent of Cases Followed Up

AUTHORS	YEAR	NUMBER OF CASES	GOOD	IMPROVED	FAIR TO POOR	RECURRENCES	MORTALITY
Allen A W	1947	196	85		15		2%
Bartels and Dulin	1943	100	86	6 7		6 7	4%
Gaster	1948	384	86	10	4	1	4 5%
Gray and Williams	1949	223	83	13	4	3 0	2 6%
Helferty	1950	178	91 5		7 2	1 2	4 5%
Hosford	1949	200	72	25	3 0		0 5%
McClure and Fallis	1940	74	78 6	13 8		4	5 3%
Miller T G and Nicholson	1946	113	92 6				
Miller Gavin	1942	230	90	10		None	3 0%
Mimpriss and Birt	1948	248	73	[illegible]	5 0	None	2 0%
Rienhoff	1945	260	78	12	8 0		2 0%
Sanders	1945	101	90		10 0		2 7%
St John et al	1948	344	85		15 0	1 5 to 1 4	2 5%
Visick	1948	505	78 7	16 4	4 9	0 9	4 8%
Walters et al	1940	212	83 5		14	2 5	1 9%
Stephenson	1948	72	87			4 0	6 9%
Watson	1947	132	81	11 4	3	2 3	9 0%

Ingelfinger[14] has summarized these consequences of gastric resection by the statement that even in the presence of some of the undesirable sequelae mentioned above a very large majority of patients are able to work and lead reasonably normal and comfortable lives As he says the residual symptoms "practically *never are so dangerous and distressing as [those] of* the disease for which the gastric resection was undertaken Most observers would be inclined to agree on this point which is certainly well supported by figures obtained from the literature

In this connection a most interesting report comes from Schoemaker[38] who has followed up 105 cases of gastrectomized patients who survived the privations of World War II and the military occupation of Holland Only ten had serious dietary difficulty in spite of the wretched food Eight patients had complaints not referable to recurrent ulcer while two had proven recurrences He knows of no gastrectomized patient who died of starvation

RESULTS OF PARTIAL GASTRECTOMY FOR BENIGN ULCER

A collection of figures from recent (1940 to 1950) reports from the United States Great Britain and Canada on the clinical results of gastrectomy is presented in Table 36 It is of course clear that the data presented do not readily fit into the Procrustean bed of a statistical table and yet no better way of presenting an over all picture seems available The figures include resections for benign ulcerating lesions without respect to location and therefore cover duodenal and gastric ulcers singly or in combination as well as jejunal ulcers In addition, some of the authors have included operations done during episodes of massive hemorrhage, thus adversely affecting the mortality rate in their reports

The length of the follow up period in the various series is somewhat variable and the percentage of patients traced likewise varies Some authors notably St John and his associates[35] have been remarkably successful in maintaining personal contact with their partially gastrectomized patients while others have relied on letters and questionnaires In spite of the introduction of these numerous variables to say nothing of individual variations in the technic and type of gastrectomy the figures show a rather remarkable degree of uniformity in at least two respects—the surgical mortality and the percentage of completely satisfied patients

The latter point may be considered first It would appear from the figures of this group of over 3500 cases that from 75 to 90 per cent of all patients subjected to gastrectomy for benign ulcer remain well with only inconsequential digestive complaints and with unimpaired working capacity Most physicians who have had the experience of working in large gastrointestinal clinics would be inclined to regard these figures for successful results as both conservative and reasonably accurate The less successful results will be considered later after some comments on figures for operative mortality

The mortality rates given in Table 36 are most impressive but must not be regarded as representative of the general experience of this country as a whole Lahey and Marshall[16] as well as St John have pointed out that in the earlier years of gastric resection for duodenal ulcer the mortality rate was 15 to 20 per cent that it was roughly halved in the period 1926 to 1935 and that in the next decade it fell to near its present level During the postwar years (1946 to 1950) the figures given from many teaching

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Bartels and Dulin	1943	100	66	6 7		6 7	4%
Gaver	1948	364	86	10	4	1	4 5%
Gray and William	1949	223	83	13	4	3 0	2 0%
Hefferty	1950	178	91 5		7 2	1 2	4 5%
Hosford	1949	200	72	25	3 0		0 5%
McClure and Fallis	1940	74	78 6	13 8		4	5 3%
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Sanders	1945	101	90		10 0		2 7%
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institutions range from 2 to 4 5 per cent while two series of cases from Veterans Administration Hospitals totalling 290 cases (reported to the writer by personal communication) had a mortality rate of about 5 per cent In contrast to these favorable figures are those given by Thompson and Prout[41] from a large municipal hospital during the war years the over all mortality rate from gastric surgery was 19 3 per cent Since this report included a group of acute perforations these figures may be somewhat misleading but the authors state that 86 per cent of the whole group of operations were gastric resections It is regrettable that more figures of this latter type are not reported since they are badly needed to complete the true picture of surgical mortality for all types of hospitals and operators

What of the 10 to 25 per cent of patients in whom results are recorded as improved" "fair or poor ? It is here that statistical surveys fall some what short of the desired result The unfavorable or relatively unsatisfactory results fall chiefly into four classifications (1) persistent nutritional diffi culties (2) motor disturbances notably the so called dumping syndrome (3) postoperative bleeding and (4) recurrences

In the main problems referable to maintaining optimum nutrition are not of a serious nature as Gaviser[9] states major difficulties from this source are rare The dumping syndrome presents a considerably more troublesome problem Perman[30] has recently remarked that the performance of more extensive resections designed particularly to protect against recurrent ulceration has increased appreciably the number of patients who suffer from "dumping" This disabling and distressing group of symptoms is dis cussed in detail in Chapter 47 No accurate information can be given as to the frequency of this complication The number of articles on the subject appearing in recent literature would indicate however that it is both common and troublesome Gaviser s report puts the incidence of "dumping" at 2 6 per cent Custer and his associates[8] in reviewing 500 consecutive gastric resections reported "dumping" in 5 6 per cent They concluded that the Schoemaker or Hofmeister type of operation furnished some protection while other writers are not convinced that the type of operation is neces sarily a factor It is curiously enough uncommon after gastric resection for carcinoma For detailed recent discussions of the subject the reader is referred to papers by Machella [0] Muir [8] Schechter and Necheles[37]

It is clear that more figures are needed to determine the true incidence of this syndrome its probable duration after operation and the type of resection least likely to produce it There are many who agree with Al varez s[4] contention that the condition is most commonly seen in hypersen sitive or psychoneurotic persons and that in some it may be present without a gastric resection It is certainly true that one does not often encounter the syndrome in the robust extroverted type of person nevertheless the preponderance of evidence is that "dumping" represents a mechanical type of disturbance rather than a psychosomatic one

So far as recurrences are concerned their reported incidence appears to depend somewhat upon the matter of definition (see p 574) Anastomotic ulcers after gastric resection do not often produce the classical ulcer se quence of symptoms and are in fact much more likely to present bizarre syndromes not easily recognizable from the patient s history as being due to ulcer Then too identification of such ulcers by roentgenologic examina tion may be uncommonly difficult Hemorrhage after resection may or may not represent the development of a recurrent lesion as various authors have

noted For these reasons many surgical authorities have been reluctant to label a patient as suffering from a recurrent ulcer until its presence has been surgically verified The actual presence of recurrence may be there fore somewhat higher than indicated by the figures in Table 36 Mage [1] whose data were obtained from personally observed cases on the gastro intestinal service at Mount Sinai Hospital, New York, puts the figure for recurrence higher than do any of the other observers For primary opera tions for duodenal ulcer he finds a minimum recurrence rate of 6 per cent, with recurrent bleeding in 7 4 per cent For secondary operations on anas tomotic ulcer the recurrence rate is 8 per cent and that for recurrent bleeding is 9 6 per cent

These discrepancies in the reported rate of recurrence remain an object of concern to all students of the subject Trimble and Lynn [43] *in their* excellent review discuss these problems and incline to the belief that a limited resection and a long loop type of anastomosis explain some of the higher recurrence rates There is good evidence to indicate that the "ade quate" radical resection is an effective deterrent to secondary or anastomotic ulceration it may on the other hand be argued that a less extensive opera tion might produce end results almost as satisfactory and avoid the motor difficulties which seem definitely more numerous and troublesome after radical procedures

In concluding this discussion of unsatisfactory results of gastrectomy mention must be made of the "antral syndrome" a chain of symptoms at *tributable to recurrent ulceration which develops when the antral mucosa* is left behind at the original operation As Moore [7] has stated these recur *rent ulcers form in at least a third of patients subjected to an inadequate* resection of this type and are peculiarly resistant to treatment

RESULTS OF RESECTION FOR GASTRIC ULCERS

These appear to be uniformly better than those for duodenal ulcer A much higher incidence of anacidity follows the operation while the inci dence of recurrence or marginal ulcer is low A figure of a 1 per cent recurrence rate seems to be fairly representative Walters and Clagett [43] reporting on 140 cases of gastric ulcer treated by partial gastrectomy stated that they found no proved case of a marginal ulcer and that of eighty five such patients answering questionnaires eighty were satisfied and in good health one to five years postoperatively Of forty nine resections for gastric ulcer reported by Kiefer [1] there were no known marginal ulcers and only five patients had free *hydrochloric acid in the gastric content postopera* tively Mage[21] reported only one recurrence in ninety eight similar cases Probably the best and most complete recent study of the results of resection for gastric ulcer is that of Ranson [3] he cites a 7 9 per cent mortality (188 cases with fifteen deaths) but 92 per cent of the patients obtained excellent to good results 5 per cent were classified as having poor results and only 3 per cent had evidence of recurrence On the basis of these and other similar *reports one is inclined to agree with those who consider the* results of resection in gastric ulcer as highly satisfactory

JEJUNAL AND GASTROJEJUNAL ULCERS

Bland Sutton (1916) was among the first to comment on the seriousness of jejunal ulcers The difficulties in dealing with this group of cases have

been commented upon by many observers since this date The high per centage of patients with anastomotic ulcers who have persistent secretion of free hydrochloric acid after resection is well known as is the tendency to repeated hemorrhage and perforation in such cases Many of these ulcers pursue an almost malignant course and their very existence as a group has profoundly influenced surgical thought and practice in dealing with all forms of peptic ulceration The necessity for treating such ulcers by wide gastric resection is generally recognized although it is agreed that this does not always effect a cure Less radical procedures are of limited use fulness as the figures presented by Walters and Clagett[4] demonstrate

Only a few authors have reviewed the end results of gastric resection in this group although the series of reports cited in Table 36 includes many operations for anastomotic lesions Priestley s and Gibson s[31] recent paper may be cited as representative They reported on 103 traced cases of gas trojejunal ulcer from a series of 283 such lesions for which gastric resection had been done five to ten years previously Excellent results were reported in 87 4 per cent of patients traced They noted as others also have that partial gastrectomy for ulcers developing after previous resection carried a higher mortality and gave less satisfactory results Visick s[44] series men tioned earlier included thirty five stomal ulcers Resection was followed by excellent results in 74 per cent of cases by poor results in 10 per cent the balance were regarded as "satisfactory Steinberg[39] reported that of seventy one patients who had had a total of 103 previous gastric operations for primary and secondary ulcer fifty seven remained well after an ade quate resection Ranson [2] reports twenty four successful gastrectomies in a group of thirty two patients with gastrojejunal ulcer It is hoped that further follow up data will become available on patients with anastomotic lesions who have had gastric resection since as a group they present a most difficult therapeutic problem (see Chap 54)

BLEEDING PEPTIC ULCERS

How great a protection against further bleeding (of either the massive or the milder chronic variety) is afforded by partial gastric resection? The question is important if only because of the fairly large group of patients operated upon for peptic ulcers which have exhibited hematemesis or melena in the past For example Gaviser s[9] previously mentioned report states that 56 per cent of the group studied had had hemorrhage as a preoperative symptom Lewison[19] reports that of 2400 patients entering The Johns Hop kins Hospital because of ulcer 10 per cent had free bleeding on admission or during their hospital stay

Walters and Cleveland[47] present a rather optimistic picture of the value of resection in this group Of a group of 135 hemorrhagic peptic ulcers (forty two duodenal twenty five gastric twelve combined duodenal and gastric and fifty six jejunal) 112 patients were successfully traced five or more years later 94 4 per cent of the group of duodenal ulcers 100 per cent of the group of gastric ulcers and 78 per cent of the jejunal group reported no further bleeding Unsatisfactory results i e further bleeding were noted in 5 per cent of the duodenal ulcer group and in 22 per cent of the jejunal ulcer series If one excludes as the authors point out a small group of patients who had the antral mucosa left *in situ* at the time of operation or who had entero anastomoses performed the over all percentage of good

control of bleeding is materially increased The risk of surgery in this group all operated upon before 1936 was about 10 per cent the authors point out that it was less than 5 per cent in a comparable series four years later If these figures may be accepted as representative it is clear that control of bleeding in all types of peptic ulcer excepting only the marginal or anastomotic variety is satisfactorily accomplished by partial gastrectomy Not all observers would agree however that such good results can be uniformly obtained and any gastro enterologist of experience can recall many patients in whom a partial gastrectomy failed to insure against further bleeding In fact a rate of recurrent bleeding as high as 25 per cent has been mentioned by some authorities

A word may be in order in regard to the mortality and results of partial gastrectomy done as an emergency measure in the face of massive hemorrhage although the condition is considered in Chapter 60 The mortality of medically treated cases of this sort is variously given as from 3 to 15 per cent obviously depending upon the age of the patient and the magnitude of the bleeding Lewison's[14] figure for mortality in The Johns Hopkins series was 8 8 per cent Numerous figures for surgical mortality on this group of cases are also available although chiefly on small groups of cases Miller[4] reported ten gastrectomies in the face of massive bleeding with no deaths Allen and Welch[3] were successful in eleven of twelve such operations These are of course exceptionally favorable figures However the mortality of surgical treatment of massive hemorrhage should not exceed 15 per cent as recent reviews by Bohrer[7] Thorstad[4] and Lewison[19] indicate It may eventually go much lower Most surgeons agree that it will be appreciably lessened if the decision to operate is made within forty eight hours of the initial hemorrhage Moore[7] has pointed out that if gastric resection is done for massive bleeding the incidence of recurrent bleeding thereafter is much higher than the incidence of demonstrable anastomotic ulcer

SUMMARY

Statistics gathered from the literature during the past ten years indicate that partial gastric resection for benign peptic ulceration deserves the high popular standing which it now enjoys It can be performed with a mortality of 2 to 5 per cent and yields essentially satisfactory results in 75 to 85 per cent of cases followed up over at least a two year period The recurrence rate appears to be low averaging about 2 5 per cent Unsatisfactory results are largely due to motor difficulties involving the stomach and jejunum these appear to be increasing somewhat in frequency as more radical resections become the fashion The operation is probably more generally satisfactory in dealing with gastric ulcer than with duodenal ulcer results in dealing with gastrojejunal ulcer still leave something to be desired Control of the bleeding ulcer is satisfactorily managed by resection especially in the case of massive hemorrhage although in this field further advances would also be welcomed

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Chapter 50

PRESENT STATUS OF VAGOTOMY

SARA M JORDAN

In 1948 the American Gastroenterological Association established a Committee for the Study of Peptic Ulcer Under the direction of two of its subcommittees nation wide surveys were begun for the study of vagotomy and of partial gastric resection in the treatment of peptic ulcer The purpose of these subcommittees was to evaluate the results (1) of vagotomy alone and *in combination with other surgical procedures* and (2) *of partial gastric* resection alone In 1950 the two subcommittees were merged to form the Subcommittee on Surgical Procedures * the purpose of which was to evaluate and compare the results of the most commonly used surgical procedures for peptic ulcer

The original vagotomy study included reports on 4076 cases of peptic ulcer a larger group of 3278 cases operated upon by surgeons in cities reporting more than fifty vagotomies and a smaller group of 798 cases reported by surgeons operating upon less than fifty cases The full report will contain

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all data on all cases The comparative data from the larger and smaller groups appear to show that the results of vagotomy alone in the hands of surgeons doing less than fifty vagotomies are not as satisfactory as those in the larger groups This may in turn have led them to perform fewer vagotomies

With the elimination of the smaller group because of incomplete follow up data the gastric ulcer cases and the cases of operative procedures other than vagotomy plus gastro enterostomy or resection (as for example pyloro plasty) the figures of 2441 cases of duodenal ulcers and 323 cases of gastro jejunal ulcers represent the cases followed to January 1950 In the follow up data collected in January 1951 1300 of these duodenal ulcers and 166 of these gastrojejunal ulcers were submitted to further study for follow up, the average duration of which was two and a half to three years The survey of subtotal gastrectomies alone showed a total of 1036 cases operated upon for duodenal ulcer and 108 cases operated upon for gastrojejunal ulcer

Since the comparative value of these procedures was the chief object of this survey it was finally decided to focus special attention on duodenal and gastrojejunal ulcers and to omit gastric ulcer from the comparative study This policy resulted from the fact that vagotomy had not been generally done for gastric ulcer because the question of malignancy made it unsafe to do it alone furthermore because of the excellent results from gastric resection alone in this type of ulcer it was generally considered unnecessary to add vagotomy to partial gastric resection Hence the comparative study was limited to duodenal and gastrojejunal ulcers only Furthermore only the three operations usually done were used in this final comparative analysis since other procedures such as pyloroplasty were not recorded in sufficiently large numbers to have statistical significance It was also observed that vagotomy alone was done in largest number in 1947 showed waning popularity in subsequent years but was combined with gastro enterostomy in increasing numbers from 1946 on The three operations chosen for comparative study are therefore (1) gastric resection alone (2) gastric resection plus vagotomy and (3) gastro enterostomy plus vagotomy The cases in all three groups had been operated upon in approximately the same surgical centers and during the same period of time January, 1946 to January 1949

The data on all these cases prepared from questionnaires filled out from personal interviews and written communications were statistically analyzed by Dr Irving Lorge of the Institute of Psychological Research Teachers College Columbia University The full report* will contain approximately 100 tables with data concerning various aspects of the problems involved

The questions regarded by the Committee as most urgently requiring answers are as follows

1 Is the operation of vagotomy or vagectomy harmful in its results on the digestive tract or other organs?

2 Is the operation of value when done without another procedure such as *gastro enterostomy or partial gastrectomy?*

3 Does the completeness of the vagotomy as determined by tests of gastric function determine the success of the operation?

4 Does it contribute a valuable additional procedure to gastro-enterostomy or resection? This question may be subdivided into two parts (*a*) Is the less radical procedure of gastro enterostomy when supplemented by

* To be published as a supplement to Gastroenterology

vagotomy made equal or superior to partial resection alone? (*b*) Is the more radical procedure of partial resection made more effective if combined with vagotomy?

The findings of this survey when analyzed statistically may be interpreted to give some information on these four points Charts have been drawn comparing multiple factors for the various operations The complication of hemorrhage was recognized as one of the baffling problems of ulcer and in this study cases with hemorrhage have been separately classified for comparative purposes

The first question concerned possible harm to the digestive tract or other organs resulting from vagotomy The first data show that the operative mortality rates in these cases varied from 0 4 to 3 2 per cent, with the exception of fifty four patients with gastric ulcer who had gastric resection plus vagotomy in whom the mortality rate was 7 4 per cent Otherwise the figures do not differ essentially from the usual average rate for gastric surgery without vagotomy The incidence of persistent gastric retention and diarrhea decreased rapidly after three months and was of little significance after the combined procedures Unless further study reveals some other untoward effects of vagotomy this study indicates that the question as to harm done by vagotomy will be answered in the negative

The results thus far seem to provide an answer to the second question Is the operation (vagotomy) of value when done without another procedure such as gastro-enterostomy or partial gastrectomy? The data indicate a definite trend away from the use of vagotomy alone in duodenal ulcer and this is true even in the hands of those surgeons who have done the largest number of vagotomies Whereas for duodenal ulcer in 1946 vagotomy alone was done in 292 cases and combined with gastro-enterostomy in 112 cases in 1948 130 patients had vagotomy alone and 353 patients vagotomy plus gastro-enterostomy The high incidence of early gastric retention (11 to 12 per cent) the long period of hospitalization (sixteen to eighteen days) and the need for subsequent drainage operations offer explanation for the waning popularity of this procedure alone in duodenal ulcer With reference to persistent gastric retention roentgenologic studies in this group of patients show that the effect on gastric motility disappears in a large number of cases after two years

The third question—Does the completeness of the vagotomy as determined by tests of gastric function determine the success of the operation?—can be answered only partially The results of gastric function tests are difficult to interpret when combined procedures are done None of the tests used in this study including the night secretion insulin and histamine tests have shown a definite correlation with the clinical subjective results

Finally there remains the question Does vagotomy contribute a valuable additional procedure to gastro enterostomy or resection? This can be further subdivided into two subdivisional questions as to (1) the relative value of gastro enterostomy plus vagotomy as compared with partial resection alone and (2) the additional value of vagotomy to partial resection These questions represent the major present day clinical problem in the surgical treatment of duodenal ulcer

The charts in this chapter show at least in some instances statistically significant differences in results from which a definite opinion may be formed regarding the results of the operations

Chart 1 shows the incidence of freedom from ulcer symptoms at the time

of the last follow up observation (1) after gastric resection alone (2) after gastric resection plus vagotomy and (3) after gastro enterostomy plus vagotomy This chart shows these results in duodenal ulcer both *without* and with previous hemorrhage The difference between gastric resection alone and gastric resection plus vagotomy is slight and statistically insignifi

Chart 1 Clinically Free of Ulcer Symptoms
Duodenal Ulcer

WITHOUT PREVIOUS HEMORRHAGE	PER CENT
Gastric resection	95 6
Gastric resection plus vagotomy	96 8
Gastro-enterostomy plus vagotomy	71 7
WITH PREVIOUS HEMORRHAGE	
Gastric resection	96 4
Gastric resection plus vagotomy	96 1
Gastro-enterostomy plus vagotomy	83 8

cant but it can be seen that the difference between these two groups and the group of gastro enterostomy plus vagotomy ranges from 12 to 25 per cent a statistically significant difference in favor of the resection procedure

Chart 2 shows the subjective results of satisfaction with operation In other *words the patient has been asked* "Are you satisfied with your operation?"

Chart 2 Satisfied with Operation
Duodenal Ulcer

WITHOUT PREVIOUS HEMORRHAGE	PER CENT
Gastric resection	93 9
Gastric resection plus vagotomy	96 9
Gastro-enterostomy plus vagotomy	94 0
WITH PREVIOUS HEMORRHAGE	
Gastric resection	91 5
Gastric resection plus vagotomy	94 8
Gastro-enterostomy plus vagotomy	93 2

and his replies have been recorded as "Yes" or "No" It will be noted here that there is no statistical difference in the three operations between the per centage of those recording themselves as satisfied with the operation in these cases of duodenal ulcer with and without previous hemorrhage In view of *the statistically significant difference shown in Chart 1 the results of* this chart are surprising and unexplained it has been suggested that those *patients interviewed while in remission would indicate* satisfaction with the operation even though there had been a previous recurrence of symptoms

Chart 3 shows the actual x ray visualization of recurrent ulcer after the three operations for duodenal ulcer Here again though a larger percentage of the gastro enterostomy plus vagotomy cases are recorded as having had recurrent ulcer by roentgenogram (2 4 and 3 6 as against 1 6 1 3 2 2 and 1 4) these differences are considered statistically not significant.

The criteria chosen from this survey in the evaluation of results are as fol lows (1) clinical freedom from ulcer symptoms (2) satisfaction with oper ation (3) ability to work or perform usual duties (4) absence of recurrent ulcer by roentgenogram (5) absence of hemorrhage in postoperative fol low up These criteria are combined to show results in Charts 4 and 7

Chart 4 shows the combined criteria for duodenal ulcer and here again

it is seen that there are definite and statistically significant differences by the five criteria just given between satisfactory results in the three operations The groups of resection and resection plus vagotomy show distinctly better results than does the group of gastro-enterostomy plus vagotomy the differ-

Chart 3 Recurrent Ulcer by Roentgenogram after Operations for Duodenal Ulcer

WITHOUT PREVIOUS HEMORRHAGE	PER CENT
Gastric resection	1 6
Gastric resection plus vagotomy	1 3
Gastro-enterostomy plus vagotomy	2.4
WITH PREVIOUS HEMORRHAGE	
Gastric resection	2 2
Gastric resection plus vagotomy	1 4
Gastro-enterostomy plus vagotomy	3 6

ence being even greater in those patients who had had previous hemorrhage than in those without previous hemorrhage

Chart 5 shows mortality figures for the three operations for duodenal ulcer The only statistically significant figure is the 5 4 per cent shown in the

Chart 4 Duodenal Ulcer Results According to Combined Criteria

WITHOUT PREVIOUS HEMORRHAGE	PER CENT
Gastric resection	86.2
Gastric resection plus vagotomy	87 2
Gastro-enterostomy plus vagotomy	80 3
WITH PREVIOUS HEMORRHAGE	
Gastric resection	87 3
Gastric resection plus vagotomy	85 0
Gastro-enterostomy plus vagotomy	75 0

gastric resection for duodenal ulcer with previous hemorrhage as compared with all other groups Approximately 25 per cent of this group showing 5 4 per cent mortality are those cases operated upon for acute hemorrhage in which because of conditions resection alone would probably be done rather than resection with the additional procedure of gastro-enterostomy

Chart 5 Duodenal Ulcer Mortality

WITHOUT PREVIOUS HEMORRHAGE	PER CENT
Gastric resection	2 5
Gastric resection plus vagotomy	2.2
Gastro-enterostomy plus vagotomy	1 4
WITH PREVIOUS HEMORRHAGE	
Gastric resection	5 4
Gastric resection plus vagotomy	1 4
Gastro-enterostomy plus vagotomy	1 0

Chart 6 shows the combined criteria as applied to gastrojejunal ulcer In this group of cases also there is a statistically significant difference in results which is unfavorable to vagotomy alone as compared with partial resection alone It is of course recognized that the latter operation is possible only when gastrojejunal ulcer has occurred after gastro-enterostomy or after a less radical partial resection

Chart 7 shows the incidence of hemorrhage (number of hemorrhages not number of patients) in the follow up study ending January 1951 It may be

noted that in duodenal ulcer those resection cases in which less than 70 per cent of the stomach was removed show poorer results than any other group while gastric resection with 70 per cent or more removal of stomach either with or without vagotomy shows the best results In the group of gastro jejunal ulcers those with history of previous hemorrhage representing a most intractable type clinically have had better results with resection alone than with vagotomy alone It is of course improbable that in gastrojejunal

Chart 6 Gastrojejunal Ulcer Results According to Combined Criteria

	PER CENT
WITHOUT PREVIOUS HEMORRHAGE	
Vagotomy alone	59 1
Gastric resection alone	81 4
WITH PREVIOUS HEMORRHAGE	
Vagotomy alone	61 6
Gastric resection alone	86 1

ulcer cases in which the marginal ulcer has occurred after a high gastric resection any other operative procedure can be done except vagotomy

The results as shown in these charts indicate (1) that the addition of vagotomy to gastric resection has not improved the subjective or objective results in duodenal ulcer over the period of observation noted (2) that sub

Chart 7 Incidence of Hemorrhages in Follow up Study
Duodenal Ulcer

	CASES	PER CENT
WITHOUT PREVIOUS HEMORRHAGE		
Gastric resection		
Less than 70 per cent resection	395	6 3
More than 70 per cent resection	455	1 3
Total of all resections	850	4 3
Gastric resection plus vagotomy	224	1 3
Gastro enterostomy plus vagotomy	872	2 1
WITH PREVIOUS HEMORRHAGE		
Gastric resection		
Less than 70 per cent resection	139	10 7
More than 70 per cent resection	47	4 2
Total of all resections	186	8 6
Gastric resection plus vagotomy	138	4 3
Gastro-enterostomy plus vagotomy	306	6 5
Gastrojejunal Ulcer		
WITHOUT PREVIOUS HEMORRHAGE		
Vagotomy alone	174	4 6
Gastric resection alone	70	5 7
WITH PREVIOUS HEMORRHAGE		
Vagotomy alone	149	19 4
Gastric resection alone	38	10 5

Note Incidence of hemorrhage refers to number of hemorrhages not number of patients

total gastric resection alone or with vagotomy has produced better results in the control of peptic ulcer than gastro enterostomy plus vagotomy and (3) that in the management of gastrojejunal ulcer subtotal gastric resection has produced better results than vagotomy alone

Further analysis of all the data including such results as the incidence of abdominal distress other than ulcer pain diarrhea and the behavior of the patients weight will be included in a later publication of the full report as a supplement to Gastroenterology

Section VI

Peptic Ulcer of the Young and the Aged

Chapter 51

GASTRIC AND DUODENAL ULCER IN INFANTS AND CHILDREN

ROGER L J KENNEDY AND JAMES W DUSHANE

Ulcers of the stomach and duodenum may occur in infants and children at any age from even before birth until puberty Perforating ulcer of the duodenum of the fetus *in utero* has been reported[13] There is some doubt whether in infants in the earlier age period such ulcers may properly be termed "peptic" In most instances they are acute lesions which either tend to heal rapidly or perforate or cause exsanguinating hemorrhage and death[11] (see also Chap 11) The evidence available suggests that with increasing age of patients ulcers tend to exhibit chronicity which permits their classification as true "peptic ulcer

ULCER IN THE NEWBORN PERIOD

Ulcer that appears in the newborn period is more apt to be duodenal than gastric, although gastric ulcer even of the perforating type has been observed in infants less than two weeks of age[8] Duodenal ulcer during this period of life usually makes its presence known by the sudden appearance of hematemesis the passage of large amounts of fresh blood from the rectum and rapidly developing signs of anemia or by evidence of perforation consisting in abdominal distention vomiting and shock Death may take place within two or three days

Diagnosis The physical findings depend upon the complications present If a massive hemorrhage into the stomach has occurred the baby may have pallor of the skin and mucous membranes generalized weakness listlessness a rapid pulse evidence of shock and bright or dark red blood in the rectum If the ulcer has perforated into the peritoneal cavity evidence of peritonitis rapidly follows producing fever abdominal distention and tenderness and evidence of paralytic ileus Perforation of the ulcer through the posterior portion of the duodenum may result in a palpable mass in the epigastrium In the rare case of an infant with chronic ulcer the physical examination reveals evidence of undernutrition and no local findings except possibly distention of the stomach as a result of pyloric obstruction The tendency of gastric ulcer in the newborn to perforate is apparently greater than the tendency of duodenal ulcer to perforate

In the period of early infancy following the neonatal period ulcers have been demonstrated which do not differ greatly in appearance or behavior from those that occur during the neonatal period For the most part they are acute and are seldom diagnosed during life unless there is gross hemorrhage obstruction or perforation Symptoms such as bleeding evidence of abdominal discomfort and vomiting occasionally of blood seem to become

more marked during this period Although such symptoms occasionally suggest the presence of ulceration deformity of the duodenum and pylorus is rare Few roentgenologic studies have been carried out which demonstrated features of ulcer in young infants

Etiology and Pathology The cause of ulcer in the neonatal and early period of infancy is unknown Sex does not appear to be a factor since ulcer occurs with about equal frequency in male and female infants That hemorrhagic disease or hemorrhagic diathesis is an important factor is disproved by the infrequent occurrence of concomitant bleeding from other parts of the body Sporadic epidemic occurrence of ulcer in young infants has been noted [7] The occurrence of ulcer in atrophic infants has received some emphasis [9] Ulcer also has been demonstrated in infants suffering from erythroblastosis fetalis [4] disease of the pancreas and liver [6] and trauma

The role played by the gastric acids in the causation of ulcer in infants is not known Gastric acidity varies during the newborn period and is said to reach its height forty eight hours after birth after which it decreases [14] but no correlation between the incidence of ulcer and the degree of acidity has been established for newborn and very young infants

The pathologic picture of ulcer in infancy (see also Chap 11) may vary although it is usually that of an acute process When the abdomen is opened at necropsy the small and large intestines may exhibit a dark purplish color due to the content of blood There may be a single ulcer or there may be two or three usually adjacent to one another The size may vary from 1 or 2 mm to a half centimeter The small ulcer may be difficult to demonstrate at necropsy and the demonstration may be made more difficult if the mucosa of the duodenum or stomach is sponged or washed in an effort to remove blood and fibrin If a clot of blood or fibrin is present and is elevated carefully a point may be discovered at which the fibrin appears to adhere to the mucosa Such a point should be sectioned microscopically allowing the blood or fibrin to remain adherent to it At times serial microscopic sections of the duodenum or the site of suspected involvement of the stomach may be necessary in order to identify the ulcer The chief histopathologic features are the loss of the mucous membrane usually complete in the involved part the presence of one or more relatively large open blood vessels and the presence of a variable number of inflammatory cells both lymphocytes and leukocytes

Treatment Treatment of ulcer in newborn infants should be directed toward the complications and should consist of general supportive measures since the infant almost invariably is acutely and severely ill If a massive hemorrhage into the stomach or duodenum has occurred efforts must be made to combat shock by the application of external warmth transfusion of whole blood intravenously and the parenteral use of fluids The administration of vitamin K is recommended Feedings by mouth are withheld until evidence of active bleeding has ceased Bleeding usually is not regarded as a surgical emergency and operative intervention is not advised because of the precarious condition of the infant Perforation of an ulcer in the newborn infant requires the same general treatment to combat shock plus antibiotics to counteract the infection which always ensues Fatal peritonitis usually occurs unless operation is performed The earlier surgical treatment is resorted to the better are the infant s chances of survival After his recovery from an ulcer special treatment is not neces

sary because recurrence is rare and the normal diet consists of frequent milk feedings anyway

Prognosis The exact prognosis of ulcer in infancy cannot be stated since there are no adequate data When brisk bleeding occurs in the newborn period the outlook depends largely upon the promptness with which transfusion of whole blood can be done The tendency to rapid loss of blood and consequent exsanguination shock and collapse of the blood vessels offers serious difficulty On the other hand the known tendency of such ulcers to heal rapidly makes it likely that such infants will survive if they can be supported by transfusions for twenty four to forty eight hours from the time bleeding appears For infants in the newborn and neonatal periods in whom perforation is the first sign of the presence of an ulcer the outlook will naturally depend upon the promptness with which surgical treatment is instituted

Whether ulcers that occur at this age persist and later give rise to signs and symptoms upon which the diagnosis of peptic ulcer can be based is *somewhat uncertain It will be necessary to observe over a period of years* those who have had definite signs of ulcer in infancy before the relationship between ulcers of infants and those of older patients can be established

ULCER IN LATER CHILDHOOD AND PUBERTY

As attention is shifted from ulcer in infancy and early childhood to ulcer in later childhood and puberty the similarity of the features of ulcer in this latter group to those in adults becomes more evident[1] Thus the tendency for the condition to predominate in males over females is clear The probable role of psychogenic and neurogenic factors in the causation of ulcer *assumes a more prominent place whereas infection vascular accidents and* anomalies may assume somewhat lesser importance as etiologic factors

It is not possible to make a reliable estimate of the incidence of peptic ulcer in the child population Data collected in the course of numerous necropsies such as those of Schmidt[17] Berglund[2] Dietrich[5] Benner[1] and Guthrie[8] summaries of case reports in the literature such as those of Holt[9] Paterson[1] and Bird Limper and Mayer[3] and Theile[18] surveys of hospitals such as that carried out by Karlstrom[10] and numerous case reports all deal with such selected groups that no conclusions can be drawn as to general incidence Nearly all authors impressed by their own experience and the obvious ease with which peptic ulcer may be overlooked in children stress the belief that *peptic ulcer occurs more commonly than available data indicate* (see also Chap 18)

Diagnosis A history of epigastric pain which appears several hours after the ingestion of a meal or occurs at night and is relieved by the ingestion of food or alkalies is the rule rather than the exception in patients aged eight or nine to fifteen years The features of pain in this age group vary considerably except in respect to location which is almost invariably epigastric The pain has been variously described as sharp burning gnawing and gripping At times the patients have complained of vague discomfort rather than actual pain There is great variation in the frequency Some of these young patients complain of pain that occurs during both the day and the night without intervals of freedom from pain Others experience pain only intermittently with intervals of days weeks or even months Still

others experience pain only when under stress, such as nervous excitement There are exceptions in respect to night pain Although by far the greater number of older children complain of night pain a significant number do not experience it The relief of pain by the ingestion of food and alkali has been noted by most of these young patients However ulcer may be present without causing pain as for example in children whose only symptoms have been tarry stools or pallor, or both Vomiting is not of common occurrence but when it does occur with frequency or regularity the presence of obstruction can be suspected as a likely complication

The diagnosis in older children who have peptic ulcer is dependent largely upon the history and roentgenologic study When the history is more or less typical roentgenologic examination almost invariably will reveal evidence of the presence of an ulcer The roentgenologic findings in children do not differ greatly from those in adults and the opinion of the trained roentgenologist can be relied upon in the great majority of cases Occasionally reliable evidence of the presence or absence of ulcer may not be obtained at the time of a first examination If there is reasonable certainty in the mind of the physician that an ulcer is present a second or even a third roentgenologic examination may be in order Rarely a peptic ulcer fails to exhibit the characteristic roentgenographic features and its presence may not be proved except by the development of complications or by direct examination of the stomach or duodenum

Gastroscopy has been used to confirm the presence of gastric ulcer and to differentiate benign from malignant lesions Because of the great infrequency of gastric ulcer in children its use is limited

Complications of peptic ulcer in children as has already been indicated are similar to those in adults Their frequency however is not great probably because of the fact that the ulcers in most instances have not been present long enough to produce cicatrization with resultant deformity and consequent obstruction or perforation of the stomach or duodenum

Differential Diagnosis This problem is minimal in patients who give a reasonably typical history of ulcer Few if any conditions in young patients will account for the ulcer syndrome except ulcer itself When the differential diagnostic problem involves the determination of what may be causing indefinite abdominal discomfort or pain which is of frequent occurrence in children roentgenologic examination of the stomach and duodenum is indicated If it reveals the presence of ulcer the conclusion will probably be reached that the cause of the trouble has been found If it fails to reveal ulcer other definite cause for the complaint may not be discovered Perhaps the commonest complaint of abdominal pain or discomfort in children is due to so called periumbilical colic This may occur at any time of the day but seldom occurs at night and rarely wakens the child from sleep Children who exhibit this complaint are apt to be of the high strung nervous type Even though such a diagnosis seems to be obvious roentgenologic examination should be carried out because the explanation of the condition may be found to be ulcer Cholecystitis cholelithiasis pancreatitis pancreatic lithiasis esophagitis and esophageal ulcer are of such uncommon occurrence in children that they seldom offer a problem of differential diagnosis

Bleeding into the gastro intestinal tract may be the only symptom of a gastro intestinal disorder If the history and course indicate that blood is

being lost in small amounts as shown by gross examination of the stools intestinal polyps ulcerative enteritis and Meckel's diverticulum may have to be eliminated as possible causes In children who experience sudden hematemesis and evidence of massive bleeding into the gastro intestinal tract the differential diagnosis usually involves exclusion of esophageal varices and peptic ulcer

Later developments in patients who suffer from peptic ulcer during child hood are matters of importance to both the patient and physician Proctor[16] reviewed 1000 cases of gastric ulcer and 1000 cases of duodenal ulcer and found that in sixteen cases of gastric ulcer and in twenty six cases of duo denal ulcer symptoms had been present since childhood If the problem is approached from another point of view that is by following patients in whom ulcers are demonstrated during childhood it becomes clear that although most of the ulcers heal in weeks or months some of the patients continue to have recurring symptoms and some experience complications which necessitate later surgical treatment

Treatment The treatment of children who suffer from peptic ulcer does not differ greatly from that used for adults (see Section IV) Rest in bed is desirable at the start of treatment This usually necessitates hospitaliza tion of the patient since it is difficult to obtain the cooperation of a child who remains at home In addition to treatment which is aimed at control of gastric acidity the administration of sedatives is indicated to insure reduction of physical activity Although antacids such as salts of sodium calcium and magnesium may be used nonabsorbable preparations of aluminum hydroxide in the form of jell or tablets as well as other prepara tions have replaced somewhat the use of some salts Medical management of children with peptic ulcer should be continued for long periods of time because the tendency to recurrence has been found in a large percentage of cases Although a considerable number of patients who suffer from peptic ulcer during childhood are destined to have surgical treatment at a later date the indications for surgical intervention during childhood are not uncommon Excision resection pyloroplasty and gastro enterostomy have been carried out in young patients To the knowledge of the authors no patient fourteen years of age or under has been treated by vagotomy

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Chapter 52

PEPTIC ULCER OF THE AGED

HENRY A RAFSKY AND MICHAEL WEINGARTEN

INCIDENCE

The great increase in the number of persons who live past the age of sixty years has resulted in considerable interest in the incidence and special problems relating to the diagnosis and treatment of peptic ulcer in this age group In 1948 12 per cent of the white population of the United States were sixty years of age or over while fifty years ago 6 6 per cent attained this age It is now recognized that peptic ulcer is no longer to be considered a disease of young and middle aged persons but rather as one which not only may continue to cause symptoms and produce dangerous complications in the aged but also frequently has its onset in persons past sixty years of age

In 1940 Mulsow[9] collected 4079 cases of peptic ulcer reported by various authors and found that 10 5 per cent occurred in persons sixty years of age or older In our own study[17] of 1800 hospital admissions for peptic ulcer 22 2 per cent of the patients had attained the age of sixty years In 1949 Mulsow[10] tabulated 2498 medically treated cases of ulcer including our own and reported an average occurrence of 22 9 per cent in persons over sixty years of age More significant perhaps is the fact that 44 2 per cent of the deaths from peptic ulcer were in patients older than sixty years

Another rather prevalent assumption which recent reports tend to dispel is that peptic ulcer in an aged person necessarily represents a continuation of a chronic process which had its onset during youth In 1941 Klingenstein[6] found that in approximately half of a group of 173 patients with gastro duodenal ulcer no symptoms had occurred until after they were fifty years of age and that an unusually large number of gastric and duodenal ulcers first manifested themselves when the patients were between the ages of sixty and seventy years In our own previously cited study of 1800 hospital cases a careful scrutiny of the history as well as inquiries from close rela

tives whenever possible indicated that 20 per cent of those who were sixty years of age or over at the time of their admission had their first symptom of ulcer after attaining the age of sixty years Levin Kirsner and Palmer[7] reported that 10 per cent of their cases of benign gastric ulcer occurred in patients past sixty five years of age almost half of whom had their first symptom after reaching sixty five years of age Kiefer and Mc Kell[8] found that in approximately half of their series of 152 patients over sixty five years ulcer apparently had its onset after they had passed their sixtieth birthday while approximately one sixth had their first symptom after reaching their seventieth birthday

Meyer and Saphir[9] refer to the possibility that aged persons may forget the history of previous gastric symptoms but on the other hand point out that at the autopsy table it is not unusual to find an acute gastric or duo denal ulcer together with a healed chronic gastric or duodenal ulcer In this connection the report of Boles and Dunbar[1] is interesting In 4000 consecutive autopsies at the Philadelphia General Hospital there were ninety seven cases of peptic ulcer observed in patients past sixty years In only ten of the ninety seven cases or about 10 per cent was a clinical diagnosis of peptic ulcer made and all ten patients had a hemorrhage or perforation which called attention to the presence of an ulcer The authors comment that "senescence results in faulty memory and old people may have strange reasons for not wishing to impart information which may lead to interference with their customary way of living It seems probable that both the incidence and rate of onset of peptic ulcer in the aged may be higher than statistical reports indicate (see also Chap 18)

ETIOLOGY

Much emphasis has been placed in the past on the increasing incidence of gastric anacidity with advancing age While there can be no question about the validity of this observation it has resulted in a tendency to con sider the likelihood of peptic ulcer in aged persons as rather remote It seems important therefore to point out the surprisingly high occurrence of hyperchlorhydria in the aged A study of the gastric secretory response[16] in forty seven relatively healthy persons over the age of sixty five none of whom had a peptic ulcer yielded the following results for free hydro chloric acid secretion after histamine stimulation

Achlorhydria	17 0%
2-19 units	27 7 %
20-34 units	10 6
35-50 units	23 5 /
51 or more units	12 7

It is apparent that from the standpoint of their ability to secrete hydro chloric acid the stomach and duodenum of aged persons may be regarded as fertile fields for the development of peptic ulcer

Neither are the psychic factors lacking Palmer[1] has stated them as follows economic dependency the feeling of being no longer wanted or needed the loss of the supporting strength represented by husband or wife or life long friends the loss of interest by the world in general in the person inactivated by age the threat of failing physical resources and of

personal security or adequacy the rebellion against the acceptance of the dependence produced by the infirmities of old age and the search for the veneration and deference which are not forthcoming

Boles[1] who is of the opinion that disturbances in circulatory mechanisms play an important part in the genesis of peptic ulcer at any age is inclined to regard the increasing incidence of ulcer in old age groups as the "result of the progressive development of vascular diseases of various types (see Chap 15) Meyer and Saphir[8] refer to the outstanding changes in the small arteries throughout the stomach wall and marked intimal thickening and reduction of the lumen of gastric vessels in their autopsied cases of gastric ulcer in aged persons

The prolonged use of indwelling tubes seems to be an important factor in the development of many acute gastric and duodenal ulcers seen at autopsy in the aged Frequently such ulcers have been found to be perforated Of sixteen patients with recent acute peptic ulcer in the sixth and later decades cited by Meyer and Saphir[8] nine had been intubated for varying lengths of time before they died An acute peptic ulcer may be found at autopsy in elderly patients who died of an acute febrile disease or in congestive heart failure or who succumbed after operations for biliary tract disease for carcinoma of the stomach and for prostatic disease Postoperative shock due to hemorrhage from an acute ulcer may erroneously be attributed to the operative procedure

HISTORY AND PHYSICAL DIAGNOSIS

Elderly patients with peptic ulcer fall into three classes (1) those in whom the disease represents a continuation of a prolonged chronic process (2) those whose first symptoms occur at an advanced age and (3) those who apply for treatment for another condition and in whom a peptic ulcer is incidentally discovered

Reference has already been made to the fact that elderly patients may have a faulty recollection of gastric symptoms and that fear of a change in their customary way of living may lead them to deny symptoms The food pain rhythm experienced by younger patients with gastric and duodenal ulcer may not be as well defined in older patients Of forty one patients over the age of sixty five with benign gastric ulcer observed by Levin Kirsner and Palmer[7] there was no relation of the pain to meals and the pain was intensified by food in eleven patients Loss of weight ranging from 10 to over 30 pounds was observed in twenty four patients Nausea vomiting and anorexia were frequently present and tarry stools were present in eighteen patients twelve of whom also had hematemesis A secondary anemia was found in twenty two patients One patient had no symptoms the lesion having been discovered during a routine x ray examination

In their analysis of 152 patients over the age of sixty five in whom a diagnosis of peptic ulcer was made Kiefer and McKell[5] found that only sixty nine patients (45 per cent) gave a characteristic history They state "Atypical symptom complexes were frequent and occurred both in patients with chronic complicated ulcers and those with brief histories of ulcer Often the complaints and physical observations were definitely misleading Nine per cent of all patients with active duodenal ulcers had tenderness in

the right upper quadrant This probably explains why four of our patients had cholecystectomies without relief of discomfort before coming to the clinic There were 12 patients with gastric and 18 with duodenal ulcer who gave a history that was typical of malignant disease of the stomach including such symptoms as pain, vomiting pronounced anorexia and loss of weight. One wonders how many elderly patients with typical symptoms of terminal stages of cancer of the stomach have been allowed to die of what was actually a benign ulcer"

Eighty one cases of peptic ulcer with onset of symptoms after sixty years of age were studied by the authors[17] The presenting symptoms and the complications encountered in this group are summarized as follows

Uncomplicated ulcer (34 cases)			
1 Pain	29		
2. Nonobstructive vomiting	4		
3. Loss of weight	1		
		34	(42 0%)
Complications (47 cases)			
1 Hemorrhage	27		
(a) Hemorrhage with mild obstruction	1		
		28	(34 6%)
2. Perforation			
(a) On admission	6		
(1) Perforation with hemorrhage	3		
(b) After admission			
(1) For coronary thrombosis	1		
(2) For urinary retention	1		
		11	(13.5%)
3 Pyloric obstruction		8	(9 9%)
		47	
Total		81	

In an aged person the differentiation between an acute episode due to coronary artery disease or to a peptic ulcer or to the coincidence of both entities may be difficult This was illustrated by the following case

Case 1 M H a man aged seventy-one years who gave a four year history of slight pyrosis was admitted to the hospital on December 24 1945 with complaints of epigastric pain radiating to the precordial region and weakness for eight days Coronary precautions were taken after an electrocardiogram showed evidence of myocardial infarction. On January 8 1946 because of persistent epigastric pain, a roentgen examination was made which showed an irregular pylorus and a spastic and irregular bulb On January 16 the epigastric pain became severe occult blood was noted in the stool and a flat roentgenogram showed free air under the diaphragm At operation a perforated gastric ulcer was found.

That the so-called "ulcer diathesis" may be observed in a person past sixty years of age was illustrated by the following case

Case 2 J S a man aged sixty-eight years with a three-year history of epigastric pain was first admitted in April 1939 with clinical evidence of a perforated ulcer The roentgen examination showed no air under the diaphragm but at operation a perforated prepyloric ulcer was found and sutured In December 1944 at the age of seventy three he was readmitted with complaint of epigastric pain for one week and vomiting and hematemesis for two weeks A roentgen study revealed a duodenal ulcer He improved on medical therapy In August 1945 he was again admitted complaining of dysphagia and vomiting immediately after meals A roentgenogram showed a funnel-shaped narrowing of the lower half of the esophagus Esophagoscopy revealed an inflammatory lesion, a biopsy of which, after dilation, was reported as showing an inflammatory ulcerating lesion of the esophagus.

Elderly patients without previous gastric complaints may have a perforation of an ulcer during the course of another illness as illustrated by the following case

Case 3 A S a man aged sixty three was admitted in May 1946 with acute urinary retention due to a hypertrophied prostate He had no previous history of dyspepsia While an intravenous pyelogram was being done he went into shock A roentgenogram showed free air under the diaphragm At operation a perforated prepyloric ulcer was found.

The natural history of peptic ulcer in the aged is similar to that in the young (see Chap 19) as long as free acid is secreted by the gastric mucosa Recurrences are frequent and complications of peptic ulcer hemorrhage obstruction and perforation occur more frequently in the aged than in the young Almost 35 per cent of the authors series of patients over sixty years of age had evidence of recent or active hemorrhage at the time of admission Thirty three of 112 patients (29 5 per cent) with duodenal ulcer in Kiefer and McKell s series had evidence of chronic obstruction In an aged patient recently observed by the authors the alkalosis was severe enough to result in a convulsive seizure and loss of consciousness so that a cerebrovascular accident was suspected prior to the patient s admission to the hospital Perforation occurred in eleven of our eighty one cases (13 5 per cent) Meyer and Saphir[8] call attention to the frequent absence of abdominal rigidity in their aged patients who after intubation had a perforated ulcer at autopsy Tanner [9] also mentions the possibility that in an aged person with a long history of pain and other ailments perforation of an ulcer may be overlooked

The physical examination of aged patients with peptic ulcer contributes little more to the diagnosis than it does in the young (see Chap 19) However complicating diseases which are an important factor in determining the therapeutic approach may be revealed by a careful physical survey Cirrhosis of the liver is a not infrequent concomitant lesion The presence of an enlarged liver in a patient with gastric ulcer may lead the observer to believe that the gastric lesion is malignant and has given rise to hepatic metastases if other evidences of cirrhosis are overlooked Hematemesis and melena in a cirrhotic patient may occasionally be due to bleeding from a peptic ulcer rather than from esophageal or gastric varices

Occasionally an elderly arteriosclerotic and hypertensive patient with no previous gastric symptoms may have a massive hemorrhage in the absence of any discoverable evidence of peptic ulcer

ROENTGENOLOGIC AND GASTROSCOPIC DIAGNOSIS

The discussion of these methods of diagnosis in Section III has general application to the problem of diagnosis in the aged Mention should perhaps be made of the greater importance of a careful differential diagnosis between benign and malignant gastric ulcer (see Chapters 25 and 29) because of the increased dangers of operation in the aged Levin and his associates[7] have found that the rate of healing of a gastric ulcer crater in the aged is slower than in the young The time required for healing in their cases was from two and one half weeks to twenty six months an average of three and one half months Therefore persistence of a crater for six to eight weeks does not in itself signify malignancy Furthermore these authors emphasize the fact that recurrent ulceration even at the same site

does not necessarily indicate malignancy and that benign gastric ulcers commonly recur at the same site

Their experience sheds an interesting light on the frequently debated question of carcinomatous degeneration of gastric ulcer They were able to observe six patients with gastric ulcer for more than ten years after the patients had reached the age of sixty five years These patients had ulcer recurrences ranging from two to nine in number but none of them at any time showed evidence of carcinomatous degeneration The authors conclude "If evidence of benign ulcer is great and frequent gastroscopic and x ray examinations are possible medical management is preferred" The difficulties of an exact differential diagnosis may be illustrated however by the fact that in six of their forty-one cases of benign gastric ulcer in aged persons a resection had to be done to establish the diagnosis



Fig 113 A Large ulcer crater in 60-year-old male B Complete healing after 3 weeks of medical treatment

Although it is now well recognized that a benign gastric ulcer may give rise to a large niche and a small ulcer be the seat of a malignant process it is still not infrequent for operation to be recommended because it is thought that a large niche indicates a malignant ulceration Figure 113 *A illustrates a large niche on the lesser curvature of a sixty year-old male* who also had a cirrhosis of the liver probably on the basis of an inadequate diet for several years Epigastric pain for six weeks was the presenting complaint Free hydrochloric acid was present, and gastroscopically the lesion appeared benign The patient was treated with a bland high protein diet frequent feedings a colloidal aluminum hydroxide preparation and both oral and parenteral vitamin supplements Three weeks later (Fig. 113 *B*) a roentgenogram showed complete disappearance of the ulcer crater Gastroscopic study subsequently showed complete healing There was no recurrence until three years later when a smaller niche was seen which also responded to medical therapy

In duodenal ulcer elderly patients with a prolonged history usually show marked roentgenologic deformity of the bulb either with or without a crater A crater when present may be large

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patient The presence of associated gastro intestinal conditions such as hiatus hernia gallbladder disease and diverticulitis of the colon usually requires a careful adjustment of diet Malnutrition is frequent among older patients with ulcer and is often due to dental difficulties and lack of ap petite Riggs et al[18] demonstrated significant deficiencies in serum total *protein albumin* and vitamin C concentration in patients with ulcer Tuohy[1] stressed the importance of a substantial protein ration a minimum of 1 gm of protein per day per kilogram of body weight Many older pa tients do not well tolerate hourly feedings of milk and cream Moreover if the family history or clinical observations indicate a tendency to athero *sclerosis* the intake *of high cholesterol foods such as egg yolk cream and* animal fats should be limited In many cases plain milk or protein hy drolysate preparations should be substituted as intermediate feedings Vitamin *supplements may* be given orally or if necessary parenterally when there is clinical evidence of deficiency malnutrition or poor appetite

Certain precautions should be observed in the administration of drugs to aged patients with ulcer The use of atropine or belladonna even in small doses may precipitate an acute glaucoma Soluble alkalies should *never* be *given to patients* with *impaired renal* function since an alkalosis may develop The aluminum hydroxide preparations are preferable The addition of magnesium trisilicate to aluminum hydroxide gel may obviate the occurrence of fecal impaction sometimes encountered in old persons when colloidal aluminum hydroxide alone is used

The objectives in the treatment of a bleeding ulcer in an elderly patient are the same as in a younger person (see Chap 60) namely to aid in the arrest of bleeding overcome shock dehydration and anemia and prevent recurrence of hemorrhage Slow intravenous administration of isotonic solution of sodium chloride and dextrose and citrated transfusions may be *used freely to combat anemia and shock without fear that any elevation of* blood pressure which may result from these therapeutic measures will have a deleterious effect

In a study[16] of the comparative severity and prognosis of gastro intestinal hemorrhage in patients with and without hypertension it was shown that *the degree of bleeding was not greater in those with hypertension Further* it was noted that the mortality of bleeding per se was not increased in those with hypertension but that the greater mortality was due to the oc currence of complications such as cerebrovascular accidents and coronary thrombosis

The *azotemia which frequently accompanies hemorrhage from ulcer in* younger patients is usually even more marked in elderly patients In the younger age group the azotemia is in almost all cases entirely prerenal[3] in nature that is it occurs in the presence of functionally intact kidneys and is due to extrarenal causes dehydration salt loss lowered blood pressure hemoconcentration and the absorption of *nitrogen from blood* which enters the intestinal lumen The urinary volume is low and the specific gravity high because the concentrating ability of the kidneys is unimpaired In elderly patients who are bleeding in addition to the pre renal factors named there is often also a renal factor They may have impaired kidney function which under normal *conditions is compensated* by an increased output of a low specific gravity urine In the presence of a *decreased circulating blood volume due to* hemorrhage this compensating

In performing a radiographic examination of the gastro intestinal tract of aged persons due regard must be given to the tendency in such persons for a rectal impaction of the ingested barium to develop Thorough catharsis followed by an enema should be prescribed at the conclusion of the examination

Advanced age is in itself no contraindication to gastroscopic examination but certain contraindications are more likely to be present in older persons They are (1) obstruction of the esophagus or of the cardia (2) aneurysm of the aorta (3) mediastinal tumors and (4) suspected esophageal varices Other conditions such as angina pectoris dyspnea severe kyphoscoliosis of the spine cardiospasm esophageal diverticulum and psychoses may also be contraindications in the aged

LABORATORY AIDS

In the determination of the gastric secretion in the aged the intramuscular injection of 0 1 mg of histamine per 10 kilograms of weight is well tolerated by aged subjects with no untoward effects Elderly patients with gastric ulcer may have low acid values but some free hydrochloric acid secretion can always be elicited after histamine stimulation in patients with benign gastric ulcer The occasional case reports of benign gastric ulcer in the presence of a histamine anacidity are based on too few examinations to permit the conclusion that the gastric mucosa in these cases was incapable of secreting free hydrochloric acid We have never observed an active duodenal ulcer in the presence of an anacidity following histamine stimulation

In a series of over 2200 cases of proved active gastric or duodenal ulcer Palmer and Nutter[13] encountered no instance of complete and persistent achlorhydria Kahn[4] did not find a single acute or chronic peptic ulcer at autopsy in 840 consecutive cases of pernicious anemia Similarly Washburn and Rozendaal found no instance of peptic ulcer in 906 consecutive cases of pernicious anemia In a study of 440 patients with pernicious anemia Murphy and Howard[11] reported four cases in which a radiologic diagnosis of duodenal ulcer was made but presented no evidence to indicate that any of the ulcers were active It seems possible that a patient with a deformed duodenal bulb due to scarring of an old ulcer may with advancing age have pernicious anemia or a histamine anacidity But we have not encountered nor have we been able to find in the literature any report of a duodenal ulcer proved to be active either by symptoms roentgenologic appearance or necropsy in a patient with a persistent histamine achlorhydria.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of gastroduodenal ulcer has been described in Chapters 25 and 26

MEDICAL TREATMENT

The uncomplicated ulcer in aged patients does not as a rule present any special therapeutic problem For details of medical regimens see Section IV However the dietary regimen must be carefully individualized in each

who "were treated at the clinic immediately after an episode of gross bleeding In six cases the hemorrhage was particularly severe and accom panied by shock *All patients were treated medically there was no opera tive intervention for acute hemorrhage and there were no deaths*"

It is our belief that if elderly patients with bleeding ulcer were routinely submitted to operation more patients would succumb who might have survived with medical therapy alone than would be saved by operation *The experience of Tanner* [9] *with surgery for benign nonperforated ulcers* in the aged tends to confirm this view He operated upon forty patients between the ages of sixty and seventy six years half of whom had a sub total gastrectomy and the rest a short circuiting operation Seven died a mortality of 17 5 per cent in patients without hemorrhage In the presence *of bleeding this mortality would undoubtedly have been increased*

Pyloric obstruction due to peptic ulcer in elderly patients often responds to medical measures (see Chap 61) Gastric aspirations and lavages anti spasmodics frequent small feedings of milk and protein hydrolysates antacids and parenteral vitamins are used Dehydration hypoproteinemia and the chemical *imbalance with due regard to potassium levels* are corrected parenterally Since the prolonged use of indwelling tubes has been known to cause acute gastric ulcers and perforations in aged subjects the methods of intermittent aspiration of Wilkinson [3] and of continuous suction of Sandweiss[19] should be used cautiously in aged subjects Relief of the obstruction indicates that it is inflammatory in origin and medical treatment may be continued Failure to relieve the obstruction indicates that it is cicatricial in nature and that operation must be performed Since pyloric obstruction rarely if ever constitutes an emergency ample time may be allowed for the most thorough preoperative preparation The gen eral condition of the patient is often such as to render gastro enterostomy preferable to subtotal gastrectomy

Perforation of a peptic ulcer requires immediate surgical intervention irrespective of the age of the patient (see Chap 63) Clinical experience has shown that the mortality rate in these cases depends largely on the time which elapses between the perforation and the operation and on the amount of gastric contents at the time of rupture While younger pa tients may in some instances be subjected to a subtotal gastrectomy simple suture of the perforation is the desirable procedure in the aged

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mechanism is impaired so that the azotemia has both renal and prerenal factors Restoration of the normal blood volume and chlorides usually results in a prompt lowering of the blood nonprotein nitrogen to normal levels provided the blood loss does not continue at a rate greater than the replacement of fluid and blood and also that prolonged anoxia has not intensified the preexisting renal or circulatory insufficiency An azotemia which persists despite fluid and blood replacement usually signifies continued bleeding or serious impairment of cardiac and/or renal function or both Thus persistent azotemia in a patient with a bleeding ulcer is a bad prognostic sign

To correct azotemia fluids must be administered orally or parenterally If there is evidence of continued bleeding it is preferable to supply fluids intravenously or by hypodermoclysis preferably the former, since the discomfort caused by a clysis may be a disturbing factor In replacing fluids care must be taken to avoid an increase in the blood volume above normal levels since this may lead to pulmonary edema In addition to administering all parenteral fluids slowly a good guide is to restrict the parenteral intake of fluid to about 3 per cent of the body weight in twenty four hours A patient who weighs 150 pounds would require approximately 2000 cc of fluid in addition to the estimated volume of blood loss Intravenous infusions may be given in the form of citrated blood of 5 per cent glucose in saline solution or in distilled water or alternately in both In determining the amount of saline to be given daily chemical determinations of the serum chlorides and a due regard for the cardiac status are essential In the presence of congestive failure the patient should be fully digitalized

The Meulengracht regimen (see Chap 60) in our opinion should not be used in the treatment of hemorrhage in elderly patients with ulcer[14] We have observed recurrence of bleeding severe pain and perforation during the course of such treatment We prefer to withhold all oral feedings and to supply fluids and vitamins parenterally until bleeding has ceased If small feedings are then well tolerated the food intake is rapidly increased

For sedation, the barbiturates are preferable to morphine during a hemorrhage Morphine often has a vagotonic effect and in the presence of bleeding particularly in elderly patients may intensify the circulatory inadequacy[2] It may also cause nausea and vomiting The barbiturates should be given in smaller than the usual doses since they are often poorly tolerated by aged persons

Almost all the deaths from hemorrhage due to peptic ulcer occur in patients over forty five years of age In this group of patients immediate surgical intervention has been advocated whenever secondary hemorrhage occurs after a short period of medical treatment However in patients over sixty years of age the occurrence of associated diseases such as cerebral and coronary artery sclerosis hypertension prostatic hypertrophy and other complicating conditions frequently adds to the dangers of surgery This renders a decision as to the advisability of continued medical treatment or surgery difficult Our experience has been that persistence with medical treatment and the liberal use of citrated blood transfusions are more often rewarded by the survival of the patient than is surgical treatment Of twenty eight patients over sixty years of age with hemorrhage from ulcer who were treated medically by the authors three or 10 7 per cent died Kiefer and McKell[5] had forty five patients over the age of sixty five years

Section VII

Peptic Ulcer Other than Gastroduodenal Ulcer

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Section VII

Peptic Ulcer Other than Gastroduodenal Ulcer

Chapter 53

ESOPHAGEAL ULCER

EDWARD B BENEDICT

DEFINITION

Peptic ulcer of the esophagus means an ulcer of the mucous membrane of the esophagus caused by the action of acid gastric juice

OCCURRENCE

The distinction should be made between true peptic ulcer of the esophagus which is rare and erosions of the esophagus which are commonly found in esophagitis Peptic ulcer of the esophagus is rare as compared with peptic ulcer of the stomach or duodenum When it does occur in the esophagus it usually involves the mucosa somewhere in the lower 10 cm It is about five times more common in men than in women and is more apt to occur in middle life

ETIOLOGY

It is probable that the presence of heterotopic gastric mucosa in the lower esophagus plays a role in the etiology It is also likely that the regurgitation of acid gastric juice through the cardiac orifice is significant The frequent association of hiatus hernia or congenitally short esophagus with esophageal ulcer tends to support this theory [1]

Associated conditions include hiatus hernia esophagitis duodenal ulcer benign stricture of the esophagus and congenitally short esophagus

COMPLICATIONS

As in peptic ulcer of the stomach and duodenum hemorrhage or perforation may occur In my experience moderate or severe hemorrhage has occurred in less than 25 per cent of the cases and has never been fatal Perforation is rare and should usually not be fatal with early diagnosis judicious use of antibiotics and exploratory thoracotomy

SYMPTOMATIC AND PHYSICAL DIAGNOSIS

The usual symptoms of esophageal ulcer are pain dysphagia odynphagia and vomiting

Pain The pain of peptic ulcer of the esophagus is usually substernal subxiphoid or high epigastric and is often accompanied by heartburn and distress It may occur at any time of the day or night and its relationship to the time of food intake is much less characteristic than the pain of gastric or duodenal ulcer It may be considerably relieved by milk soft bland

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foods and antacids but complete relief by such a regimen is less likely than in gastric or duodenal ulcer

Dysphagia means difficulty in swallowing Most patients with esophageal ulcer have some esophageal obstruction and sticking of food in the esophagus If one asks such a patient whether or not he has difficulty in swallowing he may deny any trouble in the act of swallowing and unless one asks further questions may not reveal the fact that solid food gets stuck in the



Fig 114 Roentgenogram showing ulcer crater with constricting lesion of the esophagus above hiatus hernia Esophagoscopy showed the narrowing but no ulcer was visible Biopsy however from deep within the lumen of the stricture caught the edge of the ulcer Pathology report peptic ulcer of the esophagus normal gastric mucosa

esophagus As time goes on the inflammatory process may become more acute or fibrous tissue may form to such a degree that there is also difficulty in swallowing liquids

Odynphagia means painful deglutition This is rather a common symptom of esophageal ulcer The pain is apparently associated with the passage of food over the ulcer Coarse spicy foods are more likely to cause pain than a soft bland diet

Vomiting This is a common symptom of esophageal ulcer and is probably due to the irritation of the ulcer and the esophagitis plus the stenosis almost invariably produced by the healing process It may be more of a regurgitation than an actual vomiting

Hemorrhage from peptic ulcer of the esophagus may occur in small amounts in the form of melena but is usually not a prominent symptom Massive hematemesis or melena occurs in rare instances I know of one case in which hematemesis and melena were so severe on several occasions

that surgical resection was indicated and performed during a quiescent period I also know of two cases of moderately severe melena following instrumentation

Loss of weight is almost invariably present and is due to the patient's inability to eat an adequate diet

Physical examination may show some loss of weight but is usually otherwise negative

ROENTGENOGRAPHIC DIAGNOSIS

The suspicions of the radiologist as regards peptic ulcer of the esophagus are likely to be raised by the finding of esophageal spasm delayed passage

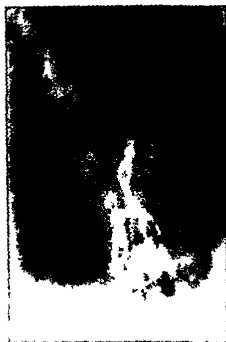


Fig 115 Roentgenogram showing pooling of barium at lower end of the esophagus with stricture X ray diagnosis benign stricture hiatus hernia esophageal ulcer and duodenal ulcer History of heartburn since childhood 3 years regurgitation and substernal pain uncontrolled by diet as well as by esophagoscopy and bougienage As is frequently the case the stricture was above the ulcer preventing endoscopic view of the ulcer Severe hemorrhage later made resection of the lower esophagus necessary

of barium narrowing of the lower esophagus hiatus hernia or short esophagus The demonstration of an ulcer crater however is difficult and depends on the taking of many spot films to show constant pooling of barium in one location (Figs 114 115) Although such constant pooling is characteristic of an ulcer crater it sometimes occurs between the esophageal folds where it may lead to an erroneous diagnosis of ulcer

ESOPHAGOSCOPIC DIAGNOSIS

The endoscopist is rarely called upon to examine a case of uncomplicated peptic ulcer of the esophagus Such cases may be suspected clinically and

roentgenologically and are then treated medically In my experience the esophagoscopist is called upon to examine and treat strictures of the esophagus which are frequently the result of peptic ulcer in that location (Figs 116 117) In such cases the stricture usually occurs at or above the level of the ulcer and prevents any view of it In rare cases a biopsy from deep within the lumen of the stricture may catch the edge of an ulcer and the pathologic report then offers conclusive proof The esophagoscopist

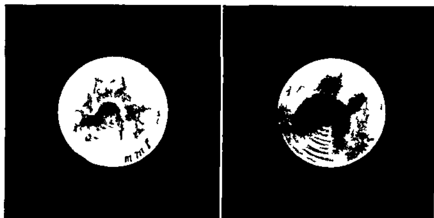


Fig 116 Esophagoscopic appearance of inflammatory stricture of the lower esophagus associated with esophageal peptic ulcer below the stricture Ulcer obscured by stricture but positive biopsy of peptic ulcer obtained Same case as shown in Figure 114

Fig 117 Esophagoscopic appearance of same case shown in Figures 114 and 116 After bouginage and medical treatment the lumen of the esophagus is much larger and the ulcer has healed

is also frequently called upon to differentiate peptic ulcer from carcinoma and achalasia (cardiospasm)

LABORATORY AIDS TO DIAGNOSIS

There are no laboratory tests which help in the diagnosis of peptic ulcer of the esophagus

DIFFERENTIAL DIAGNOSIS

Peptic ulcer of the esophagus must be differentiated from carcinoma achalasia and esophagitis

Carcinoma of the esophagus usually presents a shorter history less pain on swallowing and more continuous progression of symptoms The roentgenographic appearance of an irregular ulcerating mass in the esophagus is usually characteristic of carcinoma but in some cases of carcinoma with smooth ulceration (Figs 118 119) the differential diagnosis is not possible by roentgenogram In such cases esophagoscopy should be done and a biopsy secured from the mucosa deep within the narrowed lumen

Achalasia or cardiospasm is usually easy to differentiate from peptic ulcer of the esophagus since if it causes any pain at all it is apt to be crampy in character Moreover the history of achalasia is usually a long one of relapses and remissions The roentgenograms in achalasia charac



Fig 118 Roentgenogram showing ulcerative lesion in lower third of esophagus which has the appearance of a peptic ulcer although carcinoma could not be definitely ruled out hiatus hernia old duodenal ulcer Esophagoscopy showed polypoid carcinoma. Pathology report epidermoid carcinoma grade III History of only 7 months dysphagia in a patient of 49 should make one suspicious of carcinoma until proved otherwise Diagnosis is possible only by esophagoscopy and biopsy



Fig 119 A man aged 62 had a 14 year history (starting in 1921) of slight dysphagia substernal and back pain X ray diagnosis of esophageal ulcer hiatus hernia and duodenal ulcer was made Presence of esophageal ulcer was demonstrated by esophagoscopy and biopsy in another city Nine years later this patient came to me for treatment. My first esophagoscopy and biopsy in 1944 revealed adenocarcinoma This was resected but the patient died (aged 71) Possibly this represents a carcinoma developing in a benign peptic ulcer of the esophagus In any event it shows the difficulty of differentiating peptic ulcer of the esophagus from carcinoma

roentgenologically and are then treated medically In my experience the esophagoscopist is called upon to examine and treat strictures of the esophagus which are frequently the result of peptic ulcer in that location (Figs 116 117) In such cases the stricture usually occurs at or above the level of the ulcer and prevents any view of it In rare cases a biopsy from deep within the lumen of the stricture may catch the edge of an ulcer and the pathologic report then offers conclusive proof The esophagoscopist



Fig 116 Esophagoscopic appearance of inflammatory stricture of the lower esophagus associated with esophageal peptic ulcer below the stricture Ulcer obscured by stricture but positive biopsy of peptic ulcer obtained Same case as shown in Figure 114

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Fig 121 Roentgenogram reported by the radiologist as showing narrowing of lower esophagus with questionable diverticulum or ulceration He reported no definite evidence of cancer but could not exclude it and advised esophagoscopy Esophagoscopy 2 days later revealed 3 drams of impacted food and barium in the lower esophagus this was removed by forceps and a benign narrowing *with esophagitis was demonstrated* New roentgenograms 6 days after esophagoscopy demonstrated a foreign body in the lower esophagus reported in part as follows "Apparently it is the projection of this foreign body beyond the barium column in the esophagus which gave the appearance of an ulcer" One week after the first esophagoscopy an irregularly shaped triangular denture (2 8 by 3 0 by 3 1 cm) was removed by esophagoscopy and the patient made a good recovery Her history was of food sticking substernal pain and vomiting of 10 days duration no foreign body history

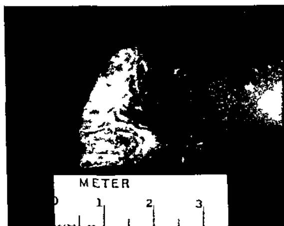


Fig 122 Photograph of denture removed from patient represented in Figure 121 and at first thought to be an esophageal ulcer by roentgenogram This case illustrates once more the difficulty in diagnosis of peptic ulcer of the esophagus

teristically reveal a dilated and sometimes tortuous esophagus with smooth conelike narrowing near the diaphragm which may suddenly release and permit ready passage of barium into the stomach Occasionally however the radiologist reports an ulcer with achalasia (Fig 120) When there is any doubt from the history and x ray examination esophagoscopy is indicated

Esophagitis without real peptic ulceration is a fairly common disease which may give rise to the same symptoms as esophageal peptic ulcer Erosions and superficial ulcerations are often present X ray examination may reveal a loss of the normal mucosal pattern with possibly slight irregu

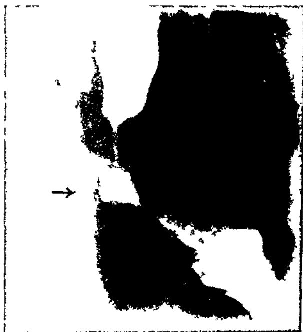


Fig 120 Roentgenogram reported as ulcer of the lower esophagus and achalasia History esophagoscopy clinical course and good response to bougienage using the Hurst mercury filled bougie practically exclude a diagnosis of esophageal ulcer This illustration is used to demonstrate the difficulty of accurate diagnosis of peptic ulcer of the esophagus by roentgenography The film probably does not represent an ulcer but puddling of barium in mucosal folds

larity and some narrowing of the lumen Esophagoscopy is indicated for direct inspection of the mucosa bougienage and biopsy to exclude carcinoma

Foreign Body A metallic foreign body in the lower end of the esophagus may occasionally project in such a way beyond the lumen of the esophagus as to make the radiologist suspect an esophageal ulcer (Fig 121) In the case illustrated in Figures 121 and 122 there was no foreign body history

MEDICAL TREATMENT

Diet The dietetic principles in uncomplicated esophageal peptic ulcer are identical with those in gastric and duodenal ulcer (see Chapters 28,

biturate is often effective, especially when given parenterally on retiring (Drugs are discussed fully in Chapter 31)

ENDOSCOPIC TREATMENT

Bouginage through the esophagoscope is of great importance in the management of the narrow lumen which frequently accompanies esophageal ulcer This should be done only by an experienced esophagoscopist In some cases bouginage may be carried out by means of a special bougie using a previously swallowed thread as a guide

SURGICAL TREATMENT

Operation is rarely indicated for benign peptic ulcer of the esophagus The possible indications are as follows

Massive Hemorrhage This is uncommon but when it occurs to an alarming degree on one or more occasions the lower end of the esophagus should be widely resected as in a cancer operation taking care to resect well above the area of inflammation An esophagogastrostomy is performed If the stoma is made near inflammatory tissue recurrences are to be expected

Perforation Major perforation of an esophageal ulcer is rare and usually requires mediastinotomy Antibiotics should be given and the patient should receive nothing by mouth and should have intravenous fluids transfusions and the like

Failure of Medical Treatment Occasionally even with the best medical management and frequent bouginage there is so much fibrosis and narrowing from the healing of an ulcer that the patient can take little besides liquids In such cases if the patient is a good surgical risk resection of the lower end of the esophagus is indicated

PREOPERATIVE AND POSTOPERATIVE CARE

Esophageal resection is a major procedure requiring the best preoperative and postoperative care In general this should be left to the surgeon doing the operation The physician in charge should cooperate by making certain that the cardiorespiratory system is adequate that the blood picture is normal (by transfusions if necessary) and that the patient's nutritional state is good The nonprotein nitrogen should be determined and other kidney function studies may be indicated

The immediate postoperative care should certainly be entirely in the hands of the surgeon After the patient has left the hospital he may be again in the hands of the physician who should advise continuation of a rather soft bland diet with complete abstinence from alcohol tobacco fried highly seasoned foods

The general principles in the preoperative and postoperative care of patients are discussed in greater detail in chapters 42 45 and 47

REFERENCE

B n h t F B and Sweet R H Benign Stricture of the Esophagus with Special Reference to Esophagitis Hiatus Hernia Esophageal Ulcer and Duodenal Ulcer Gastroenterology 11 618 1948

29 and 30) At the onset frequent milk and cream feedings should be given Later a soft bland diet, consisting of strained or finely ground food given in small amounts at frequent intervals is the most important factor in successful medical management Strongly acid or highly seasoned foods are prohibited Alcohol and tobacco should be eliminated (see Chap 32)

Sometimes patients have so much inflammation or narrowing of the esophageal lumen that only liquids can be tolerated In such cases the following schedule is recommended

7 A M	6 oz of sweetened orange juice
8 A M	10 oz of cereal water
9 A M	6 oz of chicken broth†
10 A M	6 oz of malted milk
12 noon	8 oz of cream of pea soup
1 P M	6 oz of cereal water
2 P M	6 oz of banana milk shake
3 P M	6 oz of bouillon plus beef juice†
4 P M	6 oz of eggnog
5 P M	8 oz of oyster stew (strained)†
6 P M	6 oz of orange juice
7 P M	8 oz of cream of tomato soup
8 P M	6 oz of cocoa

Cereal water is made with 1 cup of milk 1 tablespoonful of flour barley rice or wheat and 2 tablespoonfuls of sugar

† Chicken broth bouillon plus beef juice and oyster stew (strained) may be excluded in the early stages of esophageal ulcer management since they have secretagogue effects discussed in Chapters 28 29 and 30 Milk and cream soft boiled eggs strained cereal or liquid gelatin may be substituted.

This diet contains approximately 3000 calories (carbohydrates 350 gm proteins 75 gm fats 150 gm)

When the patient can tolerate a little more food others may be added straining everything through a No 25 sieve A suggested meal plan on this diet would be as follows

7 A M	Strained cereal with milk or cream
	Cocoa
8 A M	Strained orange juice with sugar
10 A M	Cereal water
12 noon	Creamed minced chicken
	Mashed potato with butter and cream
	Strained spinach with butter
	Milk with part cream
	Soft custard pudding
2 P M	Chocolate malted milk
4 P M	Tomato juice—6 oz—plus beef juice or liver pulp—2 oz
5 P M	Welsh rabbit (no bread or crackers)
	Strained beans
	Milk with cream
	Strained peaches
8 P M	Eggnog with part cream

This diet contains approximately 3100 calories (carbohydrates 350 gm proteins 85 gm fats 150 gm)

Medication Relief of pain may be obtained in some cases by sodium bicarbonate aluminum hydroxide bismuth subnitrate calcium carbonate bismuth and magnesium oxide and other antacids Atropine with a bar

biturate is often effective especially when given parenterally on retiring. (Drugs are discussed fully in Chapter 31.)

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REFERENCE

Benedict, E. B., and Sweet, R. H.: Benign Stricture of the Esophagus with Special Reference to Esophageal Hiatus Hernia, Esophageal Ulcer and Duodenal Ulcer, Gastroenterology 11: 618, 1948.

Chapter 54

POSTOPERATIVE GASTROJEJUNAL (ANASTOMOTIC) ULCER

ERNEST H GAITHER

INTRODUCTION

Gastrojejunal ulcer is of particular interest for several reasons In the first place it is the commonest of the major late sequelae of surgery for benign ulcerative lesions of the stomach and duodenum In the second place as owdon [6] has recently reminded us it is a man made disease and rep ents a serious failure of surgical treatment because too often it is a more ublesome and dangerous condition than the original disorder And ly the determination of the factors underlying late sequelae to which ojejunal ulcer is no exception is frequently the most difficult problem tro enterologic diagnosis

TERMINOLOGY

f consideration of terminology seems appropriate The terms mar omal "inastomotic "jejunal" and "gastrojejunal" are familiar to especially the last mentioned one British authorities contend ird of these secondary ulcers develop at the line of anastomosis ler in the jejunum However, many American authorities main arger majority of such lesions actually have their origin in the example Tosseland and MacDonald[40] observed that in 81 0 cases of gastrojejunal ulcer verified on pathologic examina was situated in the jejunum in 3 per cent in the stomach nt at the line of suture In the remaining 9 per cent the situa rmined because the pathologic specimen was too mutilated ended that the jejunal lesion may attain sufficient size to omosis and even in some instances to extend onto the anastomosis It is probable that the ulcerative process n and involve the suture line as the result of poor ew of present knowledge the term "jejunal ulcer" is eferred Some writers are partial to the more inclusive cer " Wilkie [40] among others is of the opinion that the istrojejunal and jejunal ulcer is more academic than pter we have used various terms as the occasion

E OF SECONDARY ULCERATION

f the literature invariably leads to the conclusion of the incidence of jejunal and gastrojejunal d no two estimates are strictly comparable It complication most frequently follows gastro luodenal ulcer much less frequently operation hat for gastric carcinoma The literature up

to a decade or so ago when gastric resection began to be favored largely was concerned with gastrojejunal ulcer following gastro-enterostomy for duodenal ulcer

The incidence of jejunal ulcer after gastro enterostomy for duodenal ulcer as reported by various observers varies widely On the one hand certain British and American surgeons such as Luff [7] Balfour [3] Smyth [37] Wilkie [46] Walton[45] and Judd and Hoerner [0] reported an incidence ranging from 2 8 to 3 9 per cent On the other hand Wright [47] Ogilvie [3] Lahey and Lewisohn [3] reported an incidence ranging from 8 5 to 34 per cent A similar disparity in incidence is seen in the statistics dealing with ulceration at or near the anastomosis following gastro enterostomy for gastric ulcer In 1917 Balfour[1] reported 100 cases of gastric ulcer in which no ulceration ensued No recurrent ulceration was noted by Walters and Clagett[43] when they reported their results in 252 cases of gastric ulcer treated by gastro enterostomy Yet Wright [47] in reporting the results in 884 cases of gastric ulcer in which gastro enterostomy was performed by various surgeons found that gastrojejunal ulcer developed subsequently in 10 45 per cent In contrast to this Wright stated that no anastomotic ulcer developed in any one of 436 patients on whom gastro-enterostomy had been performed for gastric carcinoma

One can only speculate as to this wide variation of incidence of jejunal ulcer after gastro enterostomy but certain factors which in part at least may explain the discrepancy are worthy of comment. In the first place the actual incidence cannot be determined solely on the basis of patien s who underwent operation for this complication In the second place exclusion of such a lesion on the basis of a follow up report by letter is unreliable and misleading In the third place the longer the patient is followed up after operation the greater the incidence Lastly statistics based on the inclusion of the gastric with the duodenal ulcer group make for more favorable outcome Perhaps the actual incidence of ulceration following operation for nonobstructing duodenal ulcer at the hands of all surgeons is in the neighborhood of 15 to 20 per cent as Lahey and Lowdon [0] have stated From Lewisohn s [3] reported incidence of 34 per cent the impression is gained that racial and environmental factors play a provocative role While the basis on which the statistics have been compiled can readily be challenged it also seems reasonable to presume that the lower incidence reported by surgeons of unusual skill and experience is due in considerable measure to sound surgical technic and more careful selection of patients

The incidence of jejunal ulcer following partial gastrectomy varied from 0 to 10 per cent on the basis of statistics compiled by Lahey and Swinton [4] and Scholten [30] As is to be expected the average incidence is considerably lower than that following gastro enterostomy The development of gastro jejunal ulcer following resection for gastric ulcer is strikingly infrequent Today a considerable series of cases have been reported in which no such complication occurred The occurrence of jejunal ulcer following resection for duodenal ulcer by representative American surgeons however may be as high as 6 8 per cent as shown by Kiefer s [1] report in 1942 He showed that 3 4 per cent were proved by operation and that an equal percentage were diagnosed at roentgenologic examination Thus despite the establishment of criteria for an adequate subtotal resection recurrent jejunal ulcers are found in an appreciable number of patients

The millennium with regard to the elimination of gastrojejunal ulcer promised by those who pioneered in the operation of subtotal gastric resection in the treatment of peptic ulcer has not come It is now known from bitter experience that this complication does occur in all too many cases in which the gastric mucosa is anastomosed to the small intestinal mucosa whether it be by gastro enterostomy some other conservative procedure or a more radical operation such as subtotal resection of the stomach

The incidence of gastrojejunal ulceration according to sex and age is of interest While no one can determine in advance with any degree of accuracy which patient will have the lesion young persons whose stomachs are hypertonic and empty rapidly and who have gastric hyperacidity and hypersecretion are more likely than others to have recurrence As duodenal ulcer occurs five times more frequently in males than in females it is to be expected that jejunal ulcer is encountered more frequently in the former Here again the incidence according to sex reveals considerable variation Wright[47] in Britain reported that men outnumber women 3 5 to 1 In 1227 cases collected by Ivy Grossman and Bachrach[17] ulceration occurred in 1123 males and 104 females a ratio of males to females of 10 8 to 1 Judd and Hoerner[9] dealing with a smaller series of cases reported an even higher ratio namely thirteen to one While it is reasonable to presume that jejunal ulcer is predominantly a disease of males as several authorities maintain the statistical evidence is inconclusive since the relative number of males and females on whom gastro enterostomy was performed was not stated

Ulceration following gastro enterostomy may occur at any age It has been reported in patients from two to eighty one years of age According to Wright[47] the peak incidence of ulceration is in the forty to fifty year age group according to Judd and Hoerner[9] the highest incidence was found in the third and fourth decades Most investigators are of the opinion that while jejunal ulceration can occur at almost any age the highest age incidence is in the period between thirty and fifty years the middle age period

ETIOLOGY

Many theories have been advanced to explain the cause of gastrojejunal ulcer but the fact remains that no satisfactory explanation is possible until the cause of the primary lesion is established In brief it might be said that the cause is identical with that operative in the primary ulcer plus conditions superimposed by the operation

That the susceptibility of the mucosa to damage by acid increases as the distance from the pylorus is increased has been demonstrated beyond doubt by the investigations of Mann and Bollman[9] Florey and Harding[1] and Fauley and Ivy[10] Such heightened susceptibility of the jejunal mucosa to chemical insult may be enhanced by the hyperacid and hypersecretory gastric status of the young person by any surgical procedure which permits highly acid gastric chyme to pass directly from the stomach into the jejunum without even partial neutralization by the alkaline duodenal contents and by carelessness in or total disregard of postoperative diet and postoperative medical supervision in other respects Other baneful influ

ences are emotional tension and the abuse of alcohol tobacco and condiments

Of the various mechanical factors that may give rise to ulceration at or near the anastomosis Ivy Grossman and Bachrach[16] considered the following (1) Gastric contractions tend to erode mechanically the mucosa, to interfere with the blood supply or to evaginate the stoma into the stomach. When the last named occurs it tends to contribute to the severity of both the other factors (2) The mucosa beyond the suture line is fixed to the connective tissue below and hence is more subject to trauma and has a poorer blood supply than before operation (3) The use of nonabsorbable suture material acts as a foreign body to stimulate formation of connective tissue which, for reasons just stated decreases the resistance to the corrosive action of gastric chyme Lahey and Jordan [3] in their contribution to the subject also included such factors as a stoma placed too high or one that is too small In certain circumstances surgical trauma must play an important role in the genesis of ulcers since ulcers in the line of suture as well as in the jejunum have been observed not infrequently after gastro-enterostomy in cases in which there was no clinical or pathologic evidence of a primary gastric or duodenal ulcer

SYMPTOMATOLOGY

When symptoms pain in particular more or less identical with the original manifestations recur after gastro-enterostomy or gastric resection of the Billroth II type or one of its modifications for chronic peptic ulcer the presence of a gastrojejunal ulcer should be suspected at once In the best interests of the patient he should be regarded as having such a lesion until proved otherwise Of immediate interest is the comparatively early appearance of symptoms after primary operation About 65 per cent of the patients who have the lesion following gastro-enterostomy experience their initial symptoms within two years If the patients who experience only partial or no relief are included then 75 to 80 per cent were afflicted within that period On the other hand some patients may be symptom free for twenty years or more after an operation

Various tendencies of the secondary ulcer are apparent on comparison with those of the primary lesion There is a tendency to greater severity and progressiveness of the clinical course and greater intractability to treatment *there is a lessened tendency to healing spontaneous or otherwise* there is a greater tendency to hemorrhage and to complications such as penetration perforation with formation of fistula to regional infection adhesions and contractions Clinical irregularities and complexities are introduced by virtue of these complications perforation in particular and by frequent reactivation of the original lesion which is usually a duodenal ulcer or by the occasional formation of new ulcers

Pain This is the most frequent symptom and as just indicated, is usually more severe than that caused by the original ulcer This is due chiefly to the marked tendency to penetration or perforation of the jejunal lesion As in gastric or duodenal ulcer the pain may be entirely absent throughout the course of the disease in a small percentage of cases Pain was absent in 4 per cent of Wright s[17] large series of 458 collected cases and in 14 per cent of Tosseland s[39] series of 100 cases The pain like the pain of the primary

ulcer bears a time relation to alimentation in a majority of cases Hence food or antacids afford relief although usually not to the same extent as before operation Nocturnal pain occurs in one third to one half of the cases One now generally recognized feature is the shift of pain which when present is of great diagnostic import The pain in uncomplicated jejunal or stomal ulcer tends to be diffuse and not well localized When deep penetration or perforation occurs the pain is localized to the left of the umbilicus in about 75 per cent of cases (Fig 123)

Perforation frequently gives rise to other interesting as well as disconcerting features apart from the shift in location and character of the pain The characteristic relationship of the pain to intake of food may be entirely absent as it is when a duodenal ulcer is perforating into the pancreas The

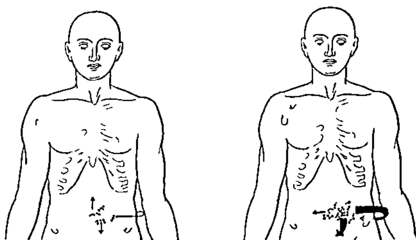


Fig 123 A Nonperforating gastrojejunal ulcers including large and subacute lesions B Perforating ulcer within or below the anastomosis Each dot indicates the point at which each patient felt the maximal distress Arrows indicate the regions to which the pain was projected the depth of shading indicates relative frequency of pain shifts (Redrawn from Rivers J A M A Vol 104)

pain may be precipitated or aggravated by certain body movements or positions or by exertion This implies involvement of the abdominal parietes colon and mesocolon by adhesions The pain may be sudden severe and knifelike and may require morphine for relief Extension of pain in perforated jejunal ulcer is downward as a rule frequently extending as low as the groins and testes To a less degree it may be projected into the left flank or back In view of these unusual features attention may be easily diverted from the gastro intestinal tract as the source of the trouble because the symptoms and signs engendered by ureteral and vesical calculi pleurisy pancreatitis "irritable colon" inflammatory and obstructive lesions of the colon sigmoid and rectum frequently are simulated Eusterman[8] reported his observations on these and other significant clinical and pathologic aspects of the disease thirty years ago Since then they have been amplified by Miller Pendergrass and Andrews[30] Rivers[34] Kiefer[21] and numerous other authorities

Uncomplicated peptic ulcer in Rivers[34] opinion probably indicates its presence as a visceral phenomenon which asserts itself over the splanchnic

nerves The projecting pain of perforating peptic ulcers is probably the result of direct stimulation of the somatic nerves with a relay of these impulses as pain into the peripheral or cutaneous branches of such nerves It is conceivable that distortion of the approved syndrome of ulcer in such instances is influenced by the accumulation of impulses of varying intensity over both the splanchnic plexuses of nerves and over the somatic nerves

Nausea and Vomiting In both small and large series of gastrojejunal ulcer as reported in the literature vomiting usually preceded by nausea occurred in 60 per cent of the patients Such vomiting may be either induced or spontaneous Vomiting of retention nature may result from mechanical obstruction malfunction of the stoma or obstruction of the proximal or distal jejunal limb Gastrojejunocolic fistula gives rise to stercoraceous vomiting

Diarrhea A purely intestinal form of symptom complex is observed occasionally This is characterized by gaseous distress located in the middle or lower part of the abdomen distention flatulency diarrhea or constipation alternating with diarrhea A lienteric type of diarrhea is usually associated with gastrojejunocolic fistula

Loss of Weight This is noted by at least one half of the patients especially those who are not receiving proper dietetic and medical care Marked loss of weight in addition to malnutrition is an invariable result of gastrojejunocolic fistula

LABORATORY AIDS TO DIAGNOSIS

As the corrosive and digestive action of the acid gastric juice undoubtedly plays an important role in the etiology of secondary ulceration a brief discussion of gastric chemism after gastro enterostomy or resection is not amiss Holman and Sandusky[1] studied the gastric secretion of seventy five clinically well patients on whom a gastro-enterostomy had been performed for peptic ulcer For this study they used histamine as a stimulus after the method of Bloomfield and Pollard The acidity and volume of secretion of sixty nine patients (92 per cent) were not reduced markedly from the preoperative level Repeated examination of six patients (8 per cent) disclosed subnormal acidity It was concluded (1) that the latter belonged to a distinct though small group in which low acid and low volume are constant findings after gastro enterostomy and (2) that these results do not support the statement that high postoperative gastric acidity lessens the chance for obtaining a satisfactory result from gastro-enterostomy Vanzant and her associates[11] further showed that the gastric acidity of patients with duodenal ulcer who after gastro enterostomy returned with jejunal ulcer was not higher than that of patients similarly operated on who after two or more years were still free from symptoms of jejunal ulcer On the basis of a new and accurate technic Vanzant and associates showed that the mean free acidity of 174 men who had jejunal ulcer was lower than normal by about 4 units

Thus it is evident that analysis of gastric secretion as usually carried out supplies limited information of diagnostic value in the absence of obstruction bleeding or achlorhydria even though the role of acid chyme in the genesis of ulcer cannot be challenged on this basis As a matter of fact there are no laboratory tests which can be considered specific in the diag

nosis of gastrojejunal ulcer However when other symptoms and signs make such lesion suspect the results of gastric analysis can help the physician in making the diagnosis In fifteen of Ginsburg and Mage's[13] twenty two patients who had bleeding late after operation and for whom analysis of gastric secretion was done free hydrochloric acid was found in appreciable amount and titer While an active anastomotic ulcer has been demonstrated occasionally in the presence of achlorhydria following conventional stimulus and aspiration Bockus[5] has properly contended that the presence of the ulcer can be excluded when achlorhydria persists during a complete fractional gastric analysis if the tip of the tube is in proper place within the body of the stomach Moreover he stated that if the initial postoperative gastric analysis shows the presence of acid the patient may be regarded as a subject for future gastrojejunal ulcer It is his practice to carry out such examination on all patients who have had gastro enterostomy or subtotal gastrectomy before their discharge from the hospital

Finally in regard to the information supplied by fractional gastric analysis Bockus considered it a most useful method in estimating the emptying function of the stomach Abnormalities are discovered in the way of either abnormal delay or rapid emptying If the partial obstruction is in the efferent loop distal to the stoma the gastric residuum may contain large amounts of bile because of stasis The residuum usually is a vivid green due to the presence of biliverdin Quantities as great as 0 5 to 1 liter may be withdrawn if dilatation of the proximal loop is marked In his opinion the recovery of such large amounts of bile is almost pathognomonic of puddling of duodenal juices usually in the proximal loop and at times in the efferent loop as the result of partial obstruction of the jejunum at a lower level

Examination of the stool for evidence of bleeding from the upper part of the digestive tract often supplies useful information This is to be expected because as Kiefer [1] and others have shown gastrojejunal ulcers are prone to present a tendency toward persistent bleeding Anemia is frequently due to this hence the rationale of blood counts single or repeated A persistent diarrhea is indication for examination of the stools for undigested food (lientery) If it is present it is a pathognomonic sign of the presence of gastrojejunocolic fistula

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

It is important to be ever mindful of the clinical fact that a gastrojejunal ulcer may develop after any type of anastomosis in which the jejunum is used whether the stomach has been resected or not With few exceptions the patient is a middle aged man who at some previous time had a short circuiting operation or resection for duodenal ulcer and after a variable period of relief has had a recurrence of trouble If the presenting complaint is more or less identical with the original one if there is a shift of pain as well as tenderness downward and to the left reaching the level of the umbilicus or below it and if in addition bleeding has been manifested for the first time the provisional diagnosis of gastrojejunal ulcer is in order In addition the demonstration of a niche or other significant abnormality at or just below the gastro enteric stoma on roentgenologic examination

usually makes such diagnosis absolute The same holds true if a crater is seen *on gastroscopic examination*

In the differential diagnosis the possibility of the presence of lesions *other than gastrojejunal* ulcer at or near the anastomosis must be considered First in order are mucosal erosions acute shallow ulcers of the stoma, gastritis gastojejunitis and jejunitis The infrequency of pain the tendency to hemorrhage are features which characterize erosions and shallow ulcerations but it is becoming increasingly apparent that the most important of all these lesions are gastrojejunitis and jejunitis

Gastro enterologic internists of much experience are under the impression that the severer forms of gastrojejunitis give rise to symptoms more or less identical with those of gastrojejunal ulcer and such a diagnosis is frequently made in the absence of roentgenologic or gastroscopic evidence of marginal or jejunal ulceration The observations of Rosenow[35] in large part failed to confirm such a clinical impression He made a histopathologic study of sixty cases of gastrojejunitis Specimens were obtained from surgically removed gastro enteric stomas In a correlation of clinical and pathologic features it was revealed that only fourteen of the sixty patients (23 per cent) had manifested a marked typical gastrojejunal ulcer like syndrome. Of these fourteen only two (14 per cent) showed severe microscopic gastrojejunitis eleven (79 per cent) showed a moderate jejunitis and one (7 per cent) showed a mild gastrojejunitis microscopically

In many instances the widest variety of diagnoses have been made among which were included malfunctioning gastro enteric stoma reactivated duodenal ulcer silent hemorrhage of uncertain origin functional gas tro intestinal disorder irritable colon mucous colitis and the like Thus in *the light of present knowledge mucosal inflammatory lesions of the gastric* stoma and upper part of the small intestine present a nondescript or vague *clinical picture moreover the severity of the symptoms is not an accurate* index of the degree of the pathologic process One exception to this generalization is the occasional instance of manifest bleeding associated with roentgenologic signs of jejunitis

The late reappearance of symptoms typical of peptic ulcer following gastro enterostomy or gastric resection makes necessary the differential diagnosis of duodenal ulcer and gastric ulcer from gastrojejunal ulcer However the incidence of the first two lesions either in the recurrent or reactivated form is considerably less than that of ulcerative and inflammatory mucosal gastrojejunal lesions For obvious reasons the recognition *of a recurrent gastric ulcer is usually not difficult However* satisfactory differentiation between a recurrent duodenal ulcer subsequent to gastro enterostomy and a gastrojejunal ulcer especially one of small size is *exceedingly difficult at times* The symptoms and signs favoring a diagnosis of duodenal or gastric ulcer for that matter are pain tenderness and as*sociated disturbances identical with those produced* by the original ulcer roentgenologic evidence of a niche in the stomach or duodenal cap actively functioning pylorus *and no significant demonstrable abnormality* in the anastomotic area

Disconcerting factors frequently intrude A gastrojejunal *ulcer may be* present in the absence of downward shift of pain and objective signs in fact, the original duodenal ulcer may be reactivated on that account A

niche in the bulb may not be demonstrable and the deformity usually present may be due to cicatrization of the original ulcer To add to our difficulties there may be some slight abnormality about the stoma or in the jejunum in the absence of roentgenologic evidence of an ulcer crater The diagnosis of a recurrent or reactivated duodenal ulcer is favored in the presence of an actively functioning pylorus other things being equal a closed pylorus is a strong deterrent to such reactivation However tran sient pyloric obstruction may occur as the result of spasm and edema engendered by the original active ulcer and the physician may errone ously assume that the pylorus has remained closed in whole or large part since the operation Assuming that the recurrent lesion is in the stomach the possibility that the lesion is actually carcinomatous must be seriously considered Gray and Lofgren[14] have shown that a high percentage of ulcerating gastric lesions which develop after gastro enterostomy are ma lignant

Disturbances arising as the result of late postoperative sequelae mainly due to technical shortcomings also require differentiation from those aris ing from the lesions just discussed Some of these sequelae will be con sidered later in this chapter with complications of gastrojejunal ulcer one of which is obstruction Space does not permit a detailed account of the many technical problems that confront the gastric surgeon at operation or the nature of the technical shortcomings and their influence on gastric func tion and form These aspects have been covered in detail by such contribu tions of those of Moynihan[31] and Balfour[2]

Disorders of the intestinal tract farther caudad than the upper part of the jejunum must receive consideration as the cause of late postoperative sequelae Included among these are appendicitis peptic ulcer in Meckel s diverticulum regional ileitis "irritable" colon chronic ulcerative colitis and gastro ileal ulcer

While disease of organs in any of the body systems can give rise to dis turbances of gastro intestinal nature such possibility is more remote in the circumstances Nevertheless pathologic changes in the cardiovascular renal system urogenital tract pulmonary and central nervous systems as well as migraine abdominal neuralgia neuritic or myositic involvement of the abdominal wall and epigastric hernia should be excluded as causative factors

ROENTGENOLOGIC DIAGNOSIS

Undoubtedly the roentgenologic diagnosis of marginal or jejunal ulcera tion is beset with more difficulties than that of the original ulcer This is due to a number of factors among which are included the deep seated location of the lesion usually involving the posterior aspect of the anas tomosis or jejunum abnormalities of inflammatory origin due to the pene trating or perforating tendency of the lesion the superimposition of coils of small intestine and the more or less unavoidable deformities resulting from the operation itself While observation of a crater apparently first demon strated in the jejunum by Barsony[4] in 1914 is essential to the absolute roent genologic diagnosis of a marginal or jejunal ulcer the impression prevailed for more than a decade that the roentgenographic examination chiefly would provide evidence of abnormality of function or form in the anastomotic area

Much dependence was placed on indirect signs such as formerly was the rule in the diagnosis of the primary ulcer Thus the lesion for a number of years escaped detection in one half to one third of the cases

With the gradual improvement in technic in particular with respect to demonstration of a crater and study of the mucosal pattern there was a corresponding increase in the accuracy of the roentgenologic diagnosis both from a positive and a negative standpoint For example Priestley and Gibson[33] in 1948 reported that observations suggestive of ulcer were made in 86 per cent of 270 cases of surgically verified gastrojejunal ulcer in which



Fig 1̲4 Flat roentgenogram of a patient who had a gastric resection with Polya anastomosis Roentgenogram failed to show presence of ulcer

roentgenologic examination was conducted However a definite roentgenologic diagnosis of such a lesion was made in only 52 per cent

It is apparent that the diagnosis of marginal or jejunal ulceration frequently is difficult In Feldman s[11] opinion the reliability of the diagnosis varies according to the care given to minute study of the stomal area Because of his lucid and comprehensive description of the various signs and characteristics of this lesion it seems advisable to quote him at length The roentgen signs of gastrojejunal and jejunal ulceration are (1) niche defect (2) mucosal changes in the stomal area (*a*) thickened mucosa (*b*) irregular nodular mucosa (3) deformity of the stoma narrowing and irregularity (4) deformity of the stomach surrounding the stoma (5) *closure* of the stoma partial or complete (6) spasticity of the stoma (7) rigidity of the stoma (8) fistulous formation (9) deformity of the jejunum narrowing and irregularity (10) gastric retention (11) jejunal retention (12) tenderness over the anastomotic area or loop of the jejunum (13) hyper



Fig 125 Lateral roentgenogram of same patient noted in Figure 124 This roentgenogram also failed to show presence of ulcer



Fig 126 Pathologic specimen of previously resected stomach of patient noted in Figure 124 The stomach was mobilized and a huge marginal ulcer the size of a silver dollar was observed on the posterior wall of the jejunum beginning at the suture line

peristalsis of the stomach (14) spasticity of the stomach (15) dilatation of the jejunum (16) spasticity of the jejunum and (17) duodenal dilatation.

The Niche Penetrating ulcers are the most common type found in gastrojejunal or jejunal ulceration The characteristics are similar to those observed in peptic ulcer elsewhere The presence of a niche is pathognomonic of ulcer The niche does not always project from the contour as in gastric ulceration but is seen as a small localized circumscribed area of increased density Absence of a niche does not exclude the presence of an ulcer even a large one as shown in Figures 124 125 and 126



Fig 127 Marginal ulcer shown *en face* through a loop of jejunum the ulcer was 1/4 inch across and 1/8 inch deep

The ulcer niche is usually single but multiple ulcers have been observed The size of the niche varies from 3 to 20 mm or more It is usually regular in outline and oval or round in contour Occasionally it may be seen as a slitlike defect The depth of the niche varies from shallow to deep Tenderness may be elicited over the niche defect Spastic manifestations are often marked The niche fills as the first small amount of barium reaches the anastomotic region It is best seen when light compression is used over the stomal and jejunal areas Complete filling of the stomach must be avoided, since this obliterates the details surrounding the stoma (Figs 127 128 129 130 and 131)

Deformity The deformity may be localized to the small ulcerated area or may be diffuse involving the stomach and jejunum adjacent to the stoma The stoma often appears tubular or funnel shaped and contracted, owing to edema and thickening secondary to inflammation The gastric



Fig 128 Ulcer about 1½ inches from the stoma on the efferent loop of the jejunum which had apparently perforated the jejunum and had adhered to and partially invaded the wall of the colon



Fig 129 Marginal ulcer following a gastrectomy Note the large ulcerous crater and the three layers—barium secretion and gas—within the niche at the arrows (Film made in the erect position) (Courtesy of Dr Maurice Feldman Clinical Roentgenology of the Digestive Tract Williams & Wilkins Co)



Fig 130 Gastro-enterostomy complicated by multiple jejunal ulceration at arrows *A* note the sacculation of the upper proximal jejunal loop also a partial obstruction in the upper jejunal loop at arrow *B* (Courtesy of Dr Maurice Feldman Clinical Roentgenology of the Digestive Tract Williams & Wilkins Co)



Fig 131 A jejunal ulcer niche defect secondary to a gastro-enterostomy shown at arrow (Courtesy of Dr Maurice Feldman Clinical Roentgenology of the Digestive Tract Williams & Wilkins Co)

contour shows slight invagination of the greater curvature at the anas tomosis and puckering of the mucosal folds An inflammatory mass may be palpated in some instances

The jejunum is irregular narrowed and retracted and the normal mark ings of the valvulae conniventes are obliterated A niche defect may or may not be visible within the deformed area The diffuse deformity of the jejunum not only involves the efferent loop but occasionally affects the af ferent segment Secondary dilatation of the jejunum proximal to the deformity is usually noted Complete obstruction may occur but partial stenosis is more common

Stoma Deformity of the stoma usually consists in puckering of the gastric contour and rugae in the anastomotic area This change is often due to associated edema and spasm The deformity of the stoma is shown roent genologically by retraction or localized slight invagination of the greater curvature This is constant and unaffected by palpatory manipulation or antispasmodic drugs Irregularities occur in the margin of the stoma A niche defect close to the stoma is frequently seen Fixation of the stoma and tenderness are of considerable diagnostic value Complete or incom plete stenosis of the stoma of a transient or permanent nature frequently occurs after gastro enterostomy Roentgenologic evidence of obstruction of the gastro enteric stoma does not necessarily indicate that there is an actual organic obstruction Repeated examinations are necessary to observe the patency of the stoma and emptying capacity of the stomach especially in the absence of retention of food or barium of considerable degree Mal function of the gastro enteric stoma may be due to a number of factors such as edema nutritional hypoproteinemia and inflammation Closure of the stoma may be due to physiologic or mechanical causes

GASTROSCOPIC DIAGNOSIS

See Chapter 55.

COMPLICATIONS

Hemorrhage Manifest bleeding occurs in about 25 per cent of chronic peptic ulcers in gastrojejunal ulcer it is somewhat increased 35 per cent on the average Melena alone occurs more frequently than hematemesis or hematemesis combined with melena Hemorrhage is seldom fatal probably because of the location of the ulcer since no large vessels are involved this is in contrast to duodenal ulcer Oozing or persistent bleeding of occult nature resulting in anemia is not uncommon It has been estimated that painless bleeding occurs in about 12 per cent of cases

Mage [8] and Ginsburg and Mage[13] made an intensive study of hemor rhage as a late sequel of gastro enterostomy and subtotal gastrectomy They noted that most patients who bled after subtotal gastrectomy also had bled before operation Six patients bled for the first time five years after the operation was performed which indicates the importance of following up patients over extended periods Mage [8] emphasized the fact that late bleed ing occurring after subtotal gastrectomy is usually due to ulceration in the jejunum and only occasionally to a newly formed lesion in the stomach Ginsburg and Mage studied eighty eight specimens removed at operation

They observed that in every case of hemorrhage associated with pain the specimen revealed a deep penetrating jejunal or gastrojejunal ulcer which showed no tendency to heal. In contrast, the specimens in cases of painless bleeding uniformly disclosed superficial jejunal or anastomotic ulcers which showed no tendency to penetrate into adjacent vessels These observers recommended conservative measures in the treatment of the latter because *of their superficial nature and tendency to heal rapidly*

Jejunitis or gastrojejunitis sometimes in association with small jejunal ulcers may give rise to hemorrhage usually of a painless nature in early adult life following a gastro-enterostomy performed during early infancy for congenital pyloric stenosis Walters[43] reported three cases of this nature more than a decade ago

Perforation Chronic subacute or acute perforation is a characteristic of the majority of jejunal ulcers for which operation is performed A jejunal ulcer which has given sufficient symptoms to justify operation usually has penetrated deeply or has perforated to some extent. Rivers[34] noted perforation in 88 per cent of jejunal ulcers at time of operation. As a result, the mesocolon and adjacent peritoneal folds are involved first in order of frequency second the colon and third the abdominal wall Such marked tendency to perforation always posing the threat of gastrojejunocolic fistula a grave complication is the best justification for early surgical intervention in cases in which symptoms are severe and intractable

On physical examination evidence of the perforation by the lesion is uniformly manifested by localized tenderness and muscle spasm This is especially so if the parietes are involved and less marked when the posterior structures are involved In former days when anterior gastro-enterostomy was occasionally performed it was not uncommon to find a tender tumefaction in the abdominal wall of inflammatory or abscess nature telltale evidence of a perforated anastomotic lesion Priestley and Gibson[32] stated that free perforation into the peritoneal cavity is unusual, an observation with which most authorities agree For example Toland and Thompson[38] accepted as authentic only ninety three cases of perforation of gastrojejunal ulcer in the literature up to 1936 and added ten cases Lowdon [6] on the other hand stated that such grave complication is comparatively common since it occurred in eighteen of sixty seven patients observed by him or his associates Perforation is more common in jejunal than in marginal ulcer and the efferent loop is involved more frequently than the afferent loop Free perforation undoubtedly follows the anterior type of anastomosis more frequently than the posterior type

Stenosis or Obstruction One form of complication of gastrojejunal ulcer following gastro enterostomy infrequently commented on is obstruction of mechanical nature giving rise to retention of food or barium of variable degree When closure of the stoma and pylorus occurs concurrently as a result of a cicatrizing duodenal ulcer the degree of obstruction may be high Gross retention following gastro-enterostomy was noted by Eusterman[8] in 25 per cent of eighty three cases of surgically verified gastrojejunal ulcer Other causes for gastric obstruction the result of faulty technic or handling of tissue by the novice must be ruled out Chief among these are extensive adhesions volvulus or herniation involving the distal or proximal jejunal loops Such complication is less frequent after resection of the

Billroth II or posterior Polya type than after gastro enterostomy Approximately 10 per cent of anastomotic ulcers produce an organic stenosis of the stoma according to Ivy and associates[18]

Roentgenologic demonstration of a nonfunctioning gastro enteric stoma while an infrequent late postoperative phenomenon is significant However it does not always imply obstruction as the result of ulceration inflammation or cicatrization of the stoma itself From a study of sixty two cases in which this sign was present preoperatively Eusterman Kirklin and Morlock[9] stated that no abnormality was noted in 10 per cent at operation in 13 per cent nonfunction was due to obstruction the result of extraneous abnormalities affecting the jejunal loop in 77 per cent gastrojejunal ulcer or gastrojejunitis was present Gastric retention was demonstrable in 80 per cent of the total number of cases in which pathologic changes were exhibited at operation but it was of considerable degree in only one third of them

Gastrojejunocolic Fistula See Chapter 57

Carcinoma of the Gastro enteric Stoma Carcinomatous transformation of a gastrojejunal ulcer is extremely rare Many authorities deny that it ever occurs granting that the primary lesion the gastric one in particular was actually benign Moreover carcinoma of the stomach could develop independently subsequent to gastro enterostomy or resection for a gastric lesion or duodenal ulcer and involve the anastomosis by direct extension Jaffe[10] reported a case of malignant stomal ulcer about 2 inches in its greatest diameter located at the anastomosis with the distal part of the greater curvature in a man fifty six years of age In 1925 an ulcer of the lesser curvature which had perforated into the pancreas was excised and an anterior gastro enterostomy with entero anastomosis had been done In 1939 this patient returned with respiratory symptoms and roentgenologic signs of pulmonary involvement The patient died and necropsy disclosed widespread metastasis to the lungs mediastinum liver and mesentery and a carcinomatous stomal ulcer It has been observed that the early stage of a stomal carcinoma simulates gastrojejunal ulcer on roentgenologic and physical examination and in its signs and symptoms In the late stage a large irregular filling defect a palpable mass and obstructive signs are suggestive of carcinoma A positive diagnosis is not always possible but the diagnosis is obvious when the greater curvature of the stomach is extensively involved

TREATMENT

Gastrojejunal ulcer like gastric or duodenal ulcer may run a mild clinical course may be amenable to medical treatment and also may heal spontaneously Many early or late temporarily painful recurrences after gastro enterostomy or gastric resection are due to such lesions which are active for variable periods and then heal Moreover as noted previously anastomotic lesions of lesser degree such as mucosal erosions acute superficial ulcers and focal mucosal inflammatory states usually respond favorably to medical measures The same is true of uncomplicated gastrojejunal ulcer although in lesser degree Medical treatment should be undertaken in the hospital where thorough sustained measures should be carried out

In some instances it may be necessary to resort to continuous intragastric drip therapy Some authorities have advocated roentgen treatment for unusually refractory lesions For details of medical treatment see Section IV

On the other hand it is becoming increasingly apparent that undue therapeutic conservatism is not in the ultimate best interests of the patient. The recognized tendency of the lesion to be refractory to treatment and the likelihood of complications must always be borne in mind Undoubtedly the majority of patients come to operation because one or more complications have developed or because of the progressively painful uncontrollable nature of the symptoms In addition the tendency to repeated recurrence of jejunal ulcer is observed in certain cases This predisposition or phenomenon is attributed to a marked "ulcer diathesis" This frequently leads to multiple operations during which successive increasing amounts of the remaining portion of the stomach are removed Gastric acidity even in an extremely small segment of the stomach of such patients usually continues *to be high presumably because of an excessive neurogenic factor in the* secretion of the acid component of the gastric juice

Because of these and other unfavorable factors inherent in the disease surgical intervention is usually necessary sooner or later in the majority of cases of gastrojejunal ulcer The former conservative surgical operations with their too frequent unsatisfactory outcome have given way to more effective radical measures which notwithstanding are attended by a low mortality in the hands of the skilled experienced surgeon The procedure now used consists in disconnection of the gastro enteric stoma excision of the stomal or jejunal ulcer and an extensive gastric resection usually with the posterior Polya type of anastomosis Note for example the satisfactory results 87.5 per cent five to ten years after operation reported by Priestley and Gibson[33] as well as the low mortality 2 9 per cent Jejunal ulcer following partial or subtotal gastrectomy is of erious import, and further resection whenever possible has been attended by high mortality

With the advent of vagotomy the medical and surgical problems of therapeutic nature have been resolved in part The short term beneficial effects of vagotomy for gastrojejunal ulcer after gastro-enterostomy have been confirmed However Walters and Fahey[44] maintained that surgical removal of the ulcer with partial gastrectomy is still the operation of choice In addition to this procedure Colp[7] advocated vagotomy Gastrojejunal ulcer following gastro-enterostomy in the young patient with hyperacidity and hypersecretion has always posed a serious problem Of course he never should have been submitted to operation in the first place except in the most extenuating circumstances Bockus[6] favored excision of such ulcers refractory to medical treatment restoration of the normal anatomy and active ulcer treatment thereafter because of unsatisfactory results following subtotal gastrectomy Vagotomy in addition would perhaps greatly reduce the high incidence of reactivation of the original duodenal ulcer or forestall a recurrent one Vagotomy promises to have its greatest usefulness in the treatment of jejunal ulcer which develops after resection of the stomach for duodenal ulcer According to Walters and Fahey[44] the short term results were excellent in 88 per cent of their cases For details of surgical treatment see Section V

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Chapter 55

GASTROSCOPIC DIAGNOSIS OF GASTROJEJUNAL ULCERS

R JOHN F RENSHAW

A true marginal or stomal ulcer is best seen through the gastroscope A jejunal ulcer may or may not be seen depending upon the distance of the ulcer from the stoma and the adequacy of visualization of the stoma and jejunum Adequate visualization of the anastomosis depends upon the type of operation, location of the stoma, the patient's body build and other factors The stomach after gastro-enterostomy or a small partial resection is usually easier to examine than the small pouch after subtotal resection Distortion and alteration of landmarks in the stomach after operation sometimes causes the gastroscopist difficulty in orientation At times the tip of the gastroscope may enter the jejunum but the risk of perforating the jejunum is not great.

The appearance of the normal gastro-enteric stoma varies greatly It is *important* that these variations be recognized and differentiated from disease processes The anastomotic opening is rarely smooth, but usually of irregular contour with serrated edges The projections from the edge may

simulate pseudopolyps or carcinoma although the latter would be rare in a stomach operated upon for benign peptic ulcer Occasionally rhythmic contractions of the stoma may be observed but usually the opening is patulous Frequently the anastomosis may be seen only from a tangential position comparable to looking across the opening of a small container held at arm s length and at eye level However when viewed more directly a segment of jejunum may be seen presenting a characteristic brownish pink or red mucosa with narrow parallel folds encircling the lumen A thin fairly clear fluid usually bubbles into the stomach with respiratory movements or jejunal contractions and may quickly obscure the view of the anastomosis Nonabsorbable sutures have been observed crossing the anastomotic line or a loose end hanging freely in the gastric lumen If the suture lies just under the *mucosa but has not cut through it the mucosa may be slightly* elevated but not inflamed On the other hand if the mucosa has been broken there is inflammation and frequently erosions Because the greatest number of such sutures are seen within a few weeks or months after operation and because there is a tendency for the sutures to slough off treatment is conservative

A gastrojejunal ulcer appears as a round or ovoid lesion with sharp *well defined edges The base is white or yellow white There may be a* narrow erythematous reaction around the edge It should be emphasized that failure to see the ulcer even with adequate visualization of the stoma does not exclude the possibility of the presence of an ulcer 1 or 2 cm beyond the stoma The findings may be entirely normal or the only clue may be regurgitation of serosanguineous fluid or excessive amounts of mucoid material Enlarged jejunal folds with marked dilatation of the *efferent loop would suggest partial obstruction distal to the point observed*

Chronic gastritis after operations on the stomach is more common than gastrojejunal ulcer and more difficult to manage As many as 50 per cent of patients examined after operation show some degree of mucosal aberration Although classified as a separate entity by gastroscopists gastritis of the stomach after operation is qualitatively similar to other types of non specific gastritis and usually is a mixture of the other types It may vary from a mild diffuse catarrhal inflammation to severe hypertrophic gastritis with verrucous nodular erosive and hemorrhagic changes The appearance of the stomach may vary not only from one patient to the next but also in the same person from time to time These mucosal abnormalities probably bear no direct relation to the development of jejunal *ulcer but they* may be responsible for symptoms attributed to chronic gastritis The minor mucosal changes do not often cause symptoms In fact one should search diligently for other causes for the symptoms before attributing them to the minor changes On the other hand severe degrees of gastritis are usually accompanied by symptoms Gross hemorrhage with jejunal ulcer may in a large part be more dependent upon bleeding from the gastritic erosions *than the ulcer*

The immediate postoperative changes consist in edema or erythema alone or in combination and localized to the region of the stoma After the third postoperative week the changes become diffuse and consist chiefly in edema erythema friability thickening and *encroachment on the stoma* It is not definitely known whether these changes would eventually develop into the more severe manifestations of chronic gastritis or not but it is

believed that in many instances hypertrophic gastritis was present before the operation and the postoperative changes were superimposed

The appearance of the gastric mucosa after vagotomy does not differ greatly from that after operation without vagotomy Vagotomy does not prevent the development of gastritic changes Lessened gastric tone and more marked alterations of landmarks for orientation in the vagotomized stomach constitute the chief difference from the nonvagotomized stomach

Chapter 56

GASTRO ILEAL ULCER*

LUCIAN A SMITH AND WALTMAN WALTERS

When the surgeon through error uses a loop of ileum in making a gastro enterostomy the resultant gastro ileal anastomosis usually leads to serious changes in the health of the patient In addition to the symptoms indicative of fistula which result from the unintentionally low anastomosis a gastro-ileal ulcer is likely to develop

It is difficult to determine the general incidence of this surgical error since all such cases may not be reported Since the first description of *gastro ileostomy in* 1915[4] *twenty four additional cases have been re* ported[1 3 7 8] Cameron and associates have studied eight more patients at the Mayo Clinic bringing the current total number of which we have knowledge to thirty three Twenty five of these are from the files of the Clinic *At the Clinic too a diagnosis of this condition is made approxi* mately once each one to two years

INCIDENCE OF GASTRO ILEOSTOMY FOR GASTROJEJUNOSTOMY

As surgical experience increased in the past decade the incidence of the erroneous anastomosis of the ileum instead of a proximal loop of jejunum to the stomach in the treatment of duodenal ulcer or pyloric ob struction decreased *The surgeon* has no difficulty in isolating the first loop of jejunum if he pulls to the right on the transverse mesocolon after the transverse colon is reflected upward The first loop of intestine that comes into the operative incision is the first loop of jejunum which can be traced easily *to its origin beneath the ligament of Treitz*

There are definite anatomic differences in the loops of jejunum and those of ileum The diameter of the intestine and thickness of its wall are larger in the former than in the latter when carefully viewed against a strong light *the blood vessels in the mesentery of the jejunum* can be seen to form primary arcades whereas in the terminal ileum the arcades are tertiary in type

With these two characteristic features which are of aid in identification

* Data in eight of our twenty five cases were studied by J M Cameron J M Waugh and M B Dockerty and will be used by Dr Cameron in his thesis in partial fulfillment of the requirements for the degree of Master of Science in Surgery from the University of Minnesota

of the first loop of jejunum it is difficult to understand how a loop of intestine far distant from the one chosen for the anastomosis can be selected and joined to the stomach Probably one of the explanations lies in the fact that occasionally even in the hands of the most experienced surgeons especially when the patient is straining under anesthesia, the first loop of jejunum is properly identified but when released, slips down among the other loops When the patient strains other loops then are forced up into the incision After the patient has ceased straining and unless the same maneuver of approaching the first loop of jejunum is followed what seems to be the first loop of jejunum but is in reality several feet distal to it may be picked up One of us (Walters) has had this happen on more than one occasion In fact on one occasion the anastomosis was made before it was discovered by checking the length of the proximal loop that the wrong loop of intestine had been used for the anastomosis When the mistake was recognized the anastomosis was taken down, the opening in the intestine closed transversely and the first loop of jejunum anastomosed to the opening in the stomach

SYMPTOMS

As might be expected the symptoms of gastro ileal ulcer are associated with those resulting from the gastro ileal anastomosis For purposes of description of the syndrome however in this chapter these symptoms will be divided into two groups and will be considered separately These statements are based on observations in twenty five cases

Symptoms Attributed to the Low Anastomosis

Loss of Weight In twenty one of the twenty five cases encountered at the Clinic loss of weight had occurred The amount lost ranged from 2 to 92 pounds (0 9 to 41 7 kg) with an average about 30 pounds (13 6 kg) in the variable intervals after gastro ileostomy There was only a rough relationship between the loss of weight and the location of the anastomosis, even though in thirteen instances the anastomosis was only 2 to 18 inches (5 to 46 cm) proximal to the ileocecal valve The loss of weight could be attributed to inadequate absorption of food due to the rapid passage of the food into the colon or to a lesser extent to vomiting There seemed to be the greatest parallelism between the loss of weight and diarrhea

Diarrhea The most distinctive feature of the diarrhea was its onset usually within the first few days after operation In a few instances frequent passage of stools was not noticed after operation until solid foods were eaten Diarrhea occurred in some instances when the anastomosis was in the middle or upper part of the ileum but it seemed most marked and most persistent in cases in which the anastomosis was lowest The passage of stools which contained undigested food soon after the operation was a symptom suggestive of the diagnosis However the stools were often fatty foamy frothy oily or just mushy or watery Bowel movements occurred most frequently right after a meal but also sometimes at night. Blood pus and mucus or associated fever were not a part of the story The lienteric and the fatty stools may be indistinguishable from those associated with gastrojejunocolic fistula but the latter is unlikely as a cause of symptoms coming so soon after operation The stools in our cases contained as

much as 62 per cent of fat by dry weight This high fat content may be suggestive of sprue or external pancreatic insufficiency except for the onset immediately after "gastro enterostomy"

Vomiting This was less common than diarrhea in our cases If pyloric *obstruction was present* and *there* was malfunction of the gastro-ileal anas tomosis vomiting of retention type occurred Observation of the vomitus was most helpful when fecal vomiting or fecal odor was present. Fecal belch occasionally occurred without vomiting

Malnutrition In addition to loss of weight malnutrition occurred in eleven of our twenty five cases This was manifested by edema weakness anorexia changes in the skin glossitis and multiple neuritis Evidence of malnutrition appeared rapidly in some of the cases but slowly or not at all in the rest The explanation must lie in the varying amount of food passing through the gastro ileal stoma When the duodenum was normal or patent even though deformed in some cases the amount of food passing into the natural channel to the small bowel was sufficient to maintain *fairly* adequate nutrition

Symptoms Referable to Gastro ileal Ulcer or Gastro ileitis

Pain Two types of pain or distress were encountered Pain of bowel type was usually low in the abdomen and was cramping It was relieved on passage of flatus or stool or by an enema. The pain due to gastro-ileal ulcer often was low or left epigastric was sometimes burning gnawing or cramp ing and had some tendency to periodicity In seven of the twelve cases in which gastro-ileal ulcer or gastro ileitis was present the pain *shifted to the* lower part of the abdomen for example to the umbilical region to the lower quadrants or to the iliac fossae When pain extended to the back with the deeper gastro-ileal ulcers it extended to the lumbar and flank regions as does the pain of *penetrating jejunal ulcers Pain thought to be due to per* sistence of or reactivation of duodenal ulcer was usually in the epigastric location with or without a shift to the right Relief of the pain by ingestion of food milk or antacid or after vomiting was suggestive of but usually atypical for ulcer pain Bloating gas distention and borborygmi were common after a low anastomosis alone or when gastro ileal ulcer was present Onset of ulcer pain due to gastro ileal ulceration was commonly delayed for a number of months after the gastro-ileostomy This is com parable to the delay which occurs before the onset of gastrojejunal ulcer after *gastro-enterostomy It is* in contrast with the onset of the lienteric diarrhea and loss of weight which are symptoms of the low anastomosis and begin soon or immediately after the operation

RESULTS OF VARIOUS EXAMINATIONS

Physical Examination Slight to moderate tenderness was present just above the umbilicus in most of our cases of gastro ileal ulcer However the principal findings were those of loss of weight weakness and dependent edema Glossitis *multiple neuritis and dry scaly skin occurred uncommonly* One patient was disoriented and after operation became jaundiced before his death Except for the slight tenderness the other findings on general examination seemed to be due to the malnutrition caused by the low anas tomosis

Roentgenologic Examination Roentgenologic examination of the stomach the colon and the small intestine or a combination of the three led to the correct location of the anastomosis or of the gastro ileal ulcer (Fig 132) in thirteen of the twenty five cases Barium was seen to enter the colon soon after leaving the stomach (Fig 133) Because of a difference in technic Brown and others[1] found that the stomach refilled after it had emptied in two of their three cases Roentgenologic examination of the colon is not as useful in demonstrating the presence of a gastro ileal anas



Fig 132 Gastro ileal ulcer

tomosis as it is in revealing the usual gastrojejunocolic fistula Attention should be called to the fact that the cholecystogram may be negated by pyloric and stomal obstruction or by the too rapid emptying of the dye into the colon where absorption is inadequate to give a satisfactory concentration in the gallbladder

Laboratory Examination In twelve cases of gastro ileal ulcer or gastro ileitis the quantity of free gastric acid after a routine test meal was greater than 22 clinical units Six patients who had no gastro ileal ulcer had achlorhydria Four had free acidity but no ulcer at the anastomosis

Studies of the stools showed excessive amounts of fat meat fibers and gross particles of undigested food As mentioned before stools which were not lienteric but contained up to 62 per cent fat (dry weight) might be incorrectly interpreted by the physician to indicate external pancreatic insufficiency sprue or gastrojejunocolic fistula When peripheral edema

was present the total serum proteins were found to be at a low level and the albumin globulin ratio was depressed Occult blood present in the stools if active ulceration was present might be from the old duodenal ulcer rather than from a gastro ileal ulcer Because of the excess fat in the stools measurements of prothrombin in the blood should be made before surgical correction is undertaken

Gastroscopic Examination Gastroscopic examination was not carried out in any of the twenty five patients There should be no more difficulty in



Fig 133 Gastro-ileostomy

demonstrating a gastro ileal ulcer than there is in seeing a gastrojejunal ulcer through the gastroscope The latter is frequently difficult however (see Chap 55)

DIFFERENTIAL DIAGNOSIS

When diarrhea occurs soon or immediately after gastro enterostomy has been performed the possibility of a low anastomosis should be considered If the stools become lienteric and fecal belching or fecal vomiting occurs it becomes obvious that there is an abnormally short communication between the colon and the stomach When these symptoms occur within the first weeks after operation it is likely that they are the result of the operation Gastrojejunocolic fistula rarely occurs earlier than four to twelve months after operation and then only after pain of recurrent ulcer which

is situated lower than the pain of the ulcer for which gastro enterostomy had been performed The time of onset is also against the likelihood of external pancreatic insufficiency or sprue Previously unrecognized infections or parasitic diarrhea may be excluded by appropriate stool and proctoscopic examinations Ulcerative colitis coming after operation is associated with blood pus and mucus in the stools and proctoscopic examination is of great value in the differential diagnosis

Vomiting due to a low gastro ileal anastomosis or gastro ileal ulcer occasionally occurs soon after operation but as a rule is a late sequel It may be of retention type if the pylorus is not patent and secondary ulceration leads to malfunction of the gastro ileal stoma In such cases the vomiting might suggest that jejunal ulceration has led to malfunction of a normally placed gastro enteric stoma unless diarrhea, loss of weight and other symptoms call attention to the low position of the anastomosis

Pain of bowel type only infrequently suggests gastro ileal ulceration but pain with any characteristics of ulcer frequently merely by its shift to the periumbilical or lower abdominal regions may indicate that a new ulcer has developed In our cases in which achlorhydria occurred there were no gastro ileal ulcers The chief difference in the shift of pain of gastro ileal ulcer from that of gastrojejunal ulcer was that in the presence of the former the pain usually shifted to a lower site

TREATMENT

Medical Treatment Medical treatment of the low gastro ileal anastomosis and gastro ileal ulcer is worthless except in preparation for surgical correction

Surgical Treatment The surgical treatment for gastro ileal anastomosis or gastro ileitis occurring subsequent to its formation consists in detaching the ileum from the opening in the stomach closing both openings the one in the ileum transversely in order not to interfere with the lumen of the ileum and thus restoring gastro intestinal continuity The next stage of the surgical procedure depends on whether the previous operation was done for duodenal ulcer In these cases it is necessary of course that the surgeon examine the duodenum to determine whether or not the scar of a healed duodenal ulcer is present If a scar is not present the possibility that the ulcer mav have been on the posterior wall and not manifest anteriorly must be considered The importance of observing whether a duodenal ulcer was present lies in the fact that 50 per cent of the patients who have gastroduodenal ulcers following gastro enterostomy for duodenal ulcer will have a recurring duodenal ulcer after the gastro enteric stoma is removed and gastro intestinal continuity is re established Walters and Clagett[9] showed this several years ago This has recently been confirmed by Priestley and Gibson[6] This observation led us during the last twenty years to perform partial gastrectomy at the time the gastro enteric anastomosis was taken down and the ulcer excised The same reasoning would apply to gastro ileal ulcers

Recently vagotomy has been performed in cases in which gastrojejunal ulcer develops after gastro enterostomy This procedure would not be applicable to the treatment of the gastro ileal ulcer hence in such cases the gastro ileal anastomosis should be taken down and gastric resection

performed if a duodenal ulcer has been present previously In two of seven cases in which one of us (Walters) disconnected the gastrojejunal anastomosis excised a gastrojejunal ulcer restored gastroduodenal and jejunal continuity and performed vagotomy recurrent duodenal ulcers developed This made it evident to us that some method of promoting emptying the stomach or reducing the amount and concentration of gastric secretion and gastric acidity must be carried out with the vagotomy in such cases

If on the other hand there does not appear to be a scar on the anterior wall of the duodenum and from the patient s history it might be assumed that an ulcer had not been present on the posterior wall of the duodenum and that the gastro enteric anastomosis had been done because of functional gastro intestinal disease removal of the gastro ileal anastomosis alone should suffice to relieve the patient s abnormal gastro intestinal symptoms which appeared after the gastro ileostomy

Although it is not the desire to introduce surgical technic to any degree in this chapter we would be amiss if we did not mention a method of removal of a gastro enteric anastomosis which we have found to be simple and effective Detachment of a loop of small intestine from the stomach can be readily accomplished by the following procedures The gastro enteric stoma is carefully dissected from the transverse mesocolon and from the attachment to the posterior parietal peritoneum and held immobile by a large gauze pack placed underneath the anastomosis Then the transverse mesocolon is dissected away from its attachment to the anastomosis so that a thin (Crile) clamp with forceful jaws can be placed across the stomach just above the site of the anastomosis The clamp when in place completely shuts off the gastric part of the anastomosis A rubber covered Doyen clamp is then placed across the small intestine just below the anastomosis An incision is made between these two instruments directly against the Crile clamp Attached to the loop of intestine thus freed is a small cuff of stomach which carries the previously made anastomosis of stomach to intestine This cuff of stomach is then excised together with a portion of the wall of the intestine making up the anastomosis In this way the area of the anastomosis is available for careful examination for inflammation and ulceration The opening in the intestine then is closed transversely in two layers in the usual way with either catgut or silk

The advantage of the clamp across the stomach near the anastomosis is that it not only prevents soiling of the operative field but prevents enlargement of the opening in the stomach after the intestine is detached When a clamp is not used in these cases expansion and contraction of the muscle layers of the stomach may produce an opening in the stomach twice the size it was when the intestine was attached The closure of the opening in the stomach can be made by continuous suture placed beneath the clamp and an additional row or two of sutures over this enfolding that primary suture If resection of the stomach or a gastro enterostomy is not to be done the opening in the transverse mesocolon can be closed by suture and it then is attached to the posterior wall of the stomach near the closed incision Thus it serves as a patch and an additional method of preventing leakage from the closed opening in the stomach

Preoperative Preparation Because of the poor general condition of many of these patients the preparation for surgical correction should include parenteral administration of water soluble vitamins as well as the oral

administration of fat soluble ones Fluids should be given parenterally if needed to reestablish normal fluid balance The level of the blood urea and blood chlorides and the carbon dioxide combining power of plasma should be determined Transfusion of whole blood is indicated for anemia and hypo proteinemia Amino acids given intravenously may be useful for patients who have hypoalbuminemia and dependent edema When the anastomosis is especially low it is wise to prepare the bowel preoperatively This can be done by giving succinylsulfathiazole (Sulfasuxidine) or aureomycin by mouth together with cleansing irrigation of the bowel

Postoperative Care This varies with the surgical procedure previously used For patients who have undergone only disconnection of the anas tomosis reasonable care and diet are necessary if duodenal ulcer had been present initially When gastric resection is performed the usual postopera tive diet should be increased more quickly than usual to hasten nutritional recovery of the patient

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Chapter 57

GASTROJEJUNOCOLIC FISTULA

FRANK H LAHEY AND CORNELIUS E SEDGWICK

INTRODUCTION

One of the most serious sequelae in the treatment of peptic ulcer by gastro jejunostomy is the formation of a gastrojejunocolic fistula It is estimated as occurring in 10 to 30 per cent of all patients with marginal ulcers who require operation[4] (Ransom 17 per cent Benedict 23 8 per cent Ver brugge 11 31 per cent Walters and Clagett 13 6 per cent) If the incidence of marginal ulcer is about 5 per cent we would expect gastrojejunocolic fistula to develop in roughly one in every 100 gastrojejunostomies performed

for peptic ulcer This is probably too high an estimate An indication that this undesirable complication is not common is the fact that no one person or clinic has reported any large group of cases in spite of the fact that during the past two or three decades many large series of gastrojejunostomies for the treatment of peptic ulcer have been performed Interestingly the incidence of duodenal ulcer is definitely less in women than in men the formation of a gastrojejunocolic fistula in a woman is indeed a rare occurrence and few cases have appeared in the literature

The primary factors responsible for the formation of a gastrojejunocolic fistula are the same as those conditions discussed elsewhere in this book that are thought to be the etiologic factors of peptic ulcer (see Chap 16) This complication may be expected more often in the patient who is the typical ulcer type in those who originally had duodenal rather than gastric ulcer and in those who originally had high gastric acidity and were most refractory to medical treatment As with marginal ulcers gastrojejunocolic fistula always follows gastrojejunostomy It is much less frequent following gastrojejunostomy combined with gastric resection than when gastrojejunostomy is instituted as the sole procedure There are also secondary causative factors relative to the technical aspects of surgically constructing a gastrojejunostomy which may predispose to the formation of a gastrojejunocolic fistula It is assumed that all gastrojejunocolic fistulas follow the formation of a marginal or jejunal ulcer If the transverse colon is closely adherent to the area of ulceration at the stoma of the stomach and jejunum one may expect adjacent inflammation to spread more rapidly to the wall of the colon with subsequent fistulous formation than if the mesenteric border of the colon is at a distance from the gastrojejunostomy For this reason it is thought that an anterior gastro-enterostomy will be followed by fewer gastrojejunocolic fistulas than posterior gastro-enterostomy For this reason if posterior gastro enterostomy is preferred it is important to bring the jejunum through the transverse mesentery as far away from the border of the colon as possible

Jejunal ulceration may occur at the stoma of a gastrojejunostomy or may occur several centimeters from the margin of the stoma Likewise a gastrojejunocolic fistula may develop close to the stoma or at a distance from it The fistula may be between the stomach and colon jejunum and colon or stomach jejunum and colon It may be small and allow little fecal material to pass into the stomach and jejunum or it may be large and divert large quantities of colon contents into the upper gastro intestinal tract The gross appearance of a gastrojejunocolic fistula at operation reveals an edematous indurated mass in the region of the transverse colon Cleavage planes are difficult to establish because of the adhesions binding the loops of bowel together Frequently the surrounding inflammation has produced a partial intermittent obstruction and both the large and small bowel may be thick walled and dilated Because of the irritating effects of the fecal material on the gastric mucosa there frequently is evidence of gastric hypertrophy

SYMPTOMATIC AND PHYSICAL DIAGNOSIS

The symptoms both subjective and objective of gastrojejunocolic fistula closely follow the physiopathology of the abnormality As the fistula de

velops secondary to a marginal or jejunal ulcer the patient has in his record the history of *a previous gastrojejunostomy or gastrectomy* At an interval varying from a few months to several years after the operation he *suffers abdominal pain* and *discomfort characteristic of a marginal ulceration* (see Chap 54) The abdominal symptoms may subside with the formation of the fistulous tract but more annoying and disagreeable symptoms develop The gastrojejunocolic fistula not only allows stomach contents to flow directly into the colon but more important allows colonic material to regurgitate into the stomach and jejunum thus *producing fecal belching and at times fecal vomiting without evidence of intestinal obstruction* Furthermore the regurgitated fecal contents cause irritation to the gastric and jejunal mucosa producing *persistent diarrhea* characteristic of this disease If the fistulous tract is large the diarrhea is severe If the fistulous tract is small and intermittently plugged with food or mucosal folds the diarrhea may be slight and intermittent

The patient with a gastrojejunocolic fistula is not only chronically ill with a poor appetite and low nutritional intake but the nutrition he does take either passes directly into the colon by passing the large absorptive area of the small bowel or if nutrition does enter the small bowel the diarrhea allows little absorption and there are subsequently large losses of water, electrolytes nutrition and vitamins The result is *severe rapid malnutrition anemia wasting avitaminosis dehydration and electrolyte imbalance*

ROENTGENOLOGIC DIAGNOSIS

The diagnosis of gastrojejunocolic fistula is usually confirmed roentgenologically after the ingestion of a barium meal or the administration of a barium enema Frequently it is difficult to demonstrate the fistula by the barium meal but failure to do so does not necessarily exclude the presence of this abnormality Failure to demonstrate the fistula after ingestion of barium in all probability is due to food particles or folds of mucosa temporarily occluding the orifice of the fistula However a barium meal is usually the first roentgenologic study in patients suspected of gastrojejunocolic fistula and although a fistulous tract may or may not be discovered this study gives one an opportunity to visualize the upper gastro intestinal tract and in many instances the niche of the marginal ulcer may be demonstrated or other upper gastro intestinal abnormalities brought to light

The second study is the administration of the barium enema As colonic regurgitation into the stomach is a frequent manifestation of gastrojejunocolic fistula the fistulous tract is usually demonstrated without difficulty Care must be taken as to the amount of barium given If the barium passes in too great a quantity from the colon into the jejunum and stomach loops of small bowel may fill too rapidly and obscure the fistulous tract As soon as the barium enters the stomach the administration of the enema must immediately be stopped

GASTROSCOPIC DIAGNOSIS

Gastroscopic examination of the stomach is rarely if ever used in the patient suspected of gastrojejunocolic fistula Furthermore to examine the stomach with the gastroscope one must inflate the stomach with air

This may be impossible with a large gastrojejunocolic fistula since the air would rapidly leak into the jejunum and colon Also most marginal ulcerations occur in the jejunum rather than in the stomach, and although a marginal ulcer on the gastric side of the gastro-enterostomy might be easily visualized, even if the gastroscope is passed through the stoma, one would have difficulty in visualizing the ulcer in the jejunum in the presence of colonic regurgitation The little information gained by gastroscopy in diagnosing gastrojejunocolic fistula does not warrant its use

LABORATORY FINDINGS

The laboratory findings in the patient with a gastrojejunocolic fistula are those changes one would expect to find in a patient with extreme malnutrition anemia avitaminosis dehydration and electrolyte imbalance Furthermore as the ingested nutrition passes rapidly through the small intestine or is diverted directly from the stomach into the colon one would expect the feces to show changes characteristic of incomplete digestion and absorption.

Blood

Blood Cell Changes Bleeding from stoma ulceration and malnutrition are evidenced by low hemoglobin and hematocrit values Dehydration may however mask this anemia, and an elevated hemoglobin and hematocrit may be misleading With great weight loss blood volume is decreased and blood volume studies will give valuable information Infection is reflected by an elevated leukocyte count and sedimentation rate

Blood Electrolyte and Fluid Changes The persistent diarrhea allows large losses of sodium potassium chlorides and bicarbonate Acidosis may develop with low serum chloride and low carbon dioxide-combining power With severe diarrhea however one must keep in mind that the main electrolyte loss is the cation sodium in excess of anions chloride or bicarbonate and that all the sodium replaced to combat this acidosis should not be in the form of sodium chloride since otherwise hyperchloremia may develop Furthermore with diarrhea, large quantities of potassium are lost and low serum potassium may develop Low serum potassium may explain on occasion an unexplained low serum chloride and high carbon dioxide the so-called hypochloremic alkalosis which may develop in these patients All these electrolyte changes must be watched for and properly interpreted so that intelligent treatment may be instituted

Blood Proteins The metabolism of proteins is greatly altered in the patient with a gastrojejunocolic fistula The intake of food is usually inadequate The food ingested is subjected to abnormal digestive processes and absorption manifested by low serum proteins and frequently a reversed albumin globulin ratio

Stools

The examination of the stools in the patient suspected of gastrojejunocolic fistula aids greatly in the diagnosis Characteristically the stools in a patient with a gastrojejunocolic fistula reflect the physiopathology of the abnormality The stools are frequently yellow and contain a high quantity of fatty acids Microscopically fecal fat should be found in undigested or

partially digested food particles Stool examination for ova and parasites should also be made to eliminate other causes of diarrhea

DIFFERENTIAL DIAGNOSIS

The weight loss and wasting associated with the gastro intestinal symptoms of gastrojejunocolic fistula frequently suggest a highly malignant intra abdominal lesion Indeed one must keep in mind the possibility of the formation of a gastrojejunocolic fistula secondary to carcinoma of the transverse colon or stomach In these cases however the history of previous gastric surgery is usually lacking Furthermore all types of gastro intestinal malignant disease are looked for and ruled out by roentgenologic studies using the barium meal and the barium enema As the most characteristic symptom is diarrhea one must distinguish between gastrojejunocolic fistula and the various diarrheas Again the diagnosis of gastrojejunocolic fistula is confirmed by roentgenologic examination If the fistulous tract is not demonstrated bacteriologic and protozoic studies of the stool must be made for possible pathogens ova and parasites which may explain the diarrhea The diagnosis is usually made without difficulty from a careful history examination and roentgenographic studies

MEDICAL TREATMENT

The treatment of gastrojejunocolic fistula is primarily surgical The medical aspects of therapy consist in preparing the patient for operation (see p 607)

SURGICAL TREATMENT

Today two plans of surgical approach to the problem of gastrojejunocolic fistula are generally accepted one advocated by Pfeiffer[3] and the other first proposed by one of us (F H L) Both plans are two stage procedures Both use a first stage procedure to divert the fecal stream away from the fistula thereby preventing colonic regurgitation into the stomach and jejunum and allowing the upper gastro intestinal tract to revert to normal Both use an interval period between stages during which the patient is allowed to return to a better nutritive state Finally both use a second stage procedure consisting in resection *en bloc* of the fistulous tract stomach jejunum and involved colon

In our method the first stage consists in diverting the fecal stream away from the fistulous tract by anastomosing the terminal ileum to the descending colon Pfeiffer s method uses an ascending colostomy as a first stage procedure to divert the fecal contents away from the fistula The interval period and second stage for all practical purposes are identical in both methods The second stage resections are formidable and difficult surgical procedures but by using these two methods of staged procedures the mortality of this serious complication of gastrojejunostomy has been greatly reduced

It is not the purpose of this book to give in detail the surgical technics involved in these procedures For those interested these technics are well described in the literature by Pfeiffer[3] and Lahey[1, 2] and may be found in standard textbooks on surgical technic

PREOPERATIVE AND POSTOPERATIVE CARE

Preoperative Care

There is no preoperative problem relative to nutrition that is more difficult to treat than the patient with a gastrojejunocolic fistula To establish a really satisfactory state of nutrition before operation is almost impossible although every attempt be made to do so As the ingested nutrition either completely by passes the large absorptive area of small bowel or passes through the small bowel rapidly little absorption takes place Consequently one must depend upon parenteral feedings

The first consideration is the replacement of fluids and electrolytes Most of these patients because of the diarrhea are dehydrated and require large quantities of fluid The amount to be replaced can be determined by the output The insensible loss of fluid through the lungs and skin is estimated to be about 1000 to 2000 cc every twenty four hours This amount added to the urinary output should be replaced by 5 per cent glucose in distilled water

One should also keep a record of the amount of diarrhea As mentioned previously diarrhea contents contain large quantities of sodium potassium chloride and bicarbonate However the cation sodium is lost in excess of the anions chloride or bicarbonate Therefore the sodium must be replaced with both chloride and bicarbonate This also prevents acidosis and helps the kidney maintain proper acid base balance A convenient solution for this purpose is Hartmann's solution which contains sodium chloride potassium chloride and in addition sodium lactate The lactate is metabolized to carbon dioxide and water and the sodium is used for replacement We recommend that the amount of fluid estimated to be lost by way of diarrhea be equally replaced with Hartmann's solution

It is also well to keep in mind the possibility of chronic potassium deficiency in these patients even though the serum potassium level and electrocardiographic changes are not indicative of such a deficit It is wise to treat prophylactically such a possible deficiency by giving 2 to 3 gm of potassium chloride in the daily infusions

The second therapeutic consideration is to give parenterally sufficient calories This is almost impossible as long as the fistula is present The infusions of 5 per cent glucose barely contain the minimum requirements Perhaps in the near future intravenous fats will be available so that large quantities of calories may be given parenterally in this form Such a solution will be a great aid in these wasted patients

An attempt is always made to replace proteins The use of hydrolysates such as amigen or the use of amino acid solutions has been disappointing since these substances are usually burned as calories rather than used for the synthesis of body proteins Blood and plasma are better sources of protein replacement If serum proteins are greatly reduced one of the best methods available to replace them is human serum albumin In a period of two or three days one may elevate subnormal serum proteins to normal values by giving frequent infusions of human serum albumin

Anemia is always present and is treated most effectively by large quantities of whole blood transfusions An attempt is always made to bring the hematocrit erythrocyte count and hemoglobin values up to normal Frequently because of wasting and dehydration these values may be high

and may not be a true index of the amount of blood to replace Blood volume determinations would be of more value Since blood volume determinations are not made in many hospitals however a working guide is to use about 40 cc of whole blood for every pound of body weight lost

The nutritional status of these patients is associated with severe avitaminosis The avitaminosis is treated preoperatively with large doses of vitamin B complex and vitamins C and K We routinely give an ampule of solu B 500 mg of cevitamic acid and 72 mg of hyquinone daily

The ordinary methods of medically treating patients with marginal ulcer discussed elsewhere in this book are of no particular value once a gastrojejunocolic fistula has developed Morphine occasionally is of aid in treating the pain and diarrhea associated with the fistula but there is no medical therapy which offers a cure to these patients since its effects are the result of altered intestinal mechanics

We cannot overemphasize the importance of careful preoperative preparation of these seriously ill patients if a reasonable mortality and morbidity are to be expected after surgery

Postoperative Care

Once these patients have had a satisfactory first stage procedure diverting the fecal stream away from the fistula their nutritive state improves greatly The diarrhea subsides almost immediately Food is readily ingested and absorption and digestive processes revert to normal A few days after operation the patients are placed on feeding regimens similar to those used for the treatment of marginal ulcer discussed elsewhere The patient s nutrition rapidly improves and in a period varying from one month to several months he is ready for the second stage procedure It is not uncommon during this interval for the fistulous tract to close and the marginal ulceration to heal partially We believe however that all these patients should be subjected to resection of the stomach jejunum and colon if permanent satisfactory results are to be obtained Preparing the patient for the secondary stage and the care following resection are the same as the preoperative and postoperative care used with gastrectomy

CASE HISTORIES

Case 1 A man fifty four years of age first came to the Clinic in 1940 because of colitis From 1923 to 1929 he had suffered from epigastric pain and a diagnosis of duodenal ulcer was made In January 1928 he had a mild hemorrhage In October 1929 a gastro-enterostomy was performed For two years he was completely free from pain and distress From 1931 to 1934 he had several small hemorrhages From 1934 to 1937 usually twice a year October and May he passed small amounts of blood In 1936 he had from six to twenty bowel movements daily In 1937 a roentgenogram revealed a fistula between the jejunum and colon At the time of admission to the Lahey Clinic the frequency of bowel movements had increased and he had noticed a mass in the abdomen A diagnosis of gastrojejunocolic fistula was made In July 1940 an ileocolostomy was performed The terminal ileum was anastomosed to the descending colon Postoperatively he responded well His appetite returned and his bowels were moving only once a day at the time of discharge

The patient returned to the hospital three months later at which time the second stage procedure was performed consisting in removal of the right colon transverse colon stomach and jejunum (Fig 134) After this procedure he did well except for intestinal obstruction caused by adhesions This required another operation for lysis of adhesions Thereafter he did exceedingly well and has not had any trouble up to the present time

Case 2 A man aged forty eight years had the signs and symptoms of duodenal ulcer in 1931 In 1939 a subtotal gastrectomy with a posterior gastro-enterostomy was per

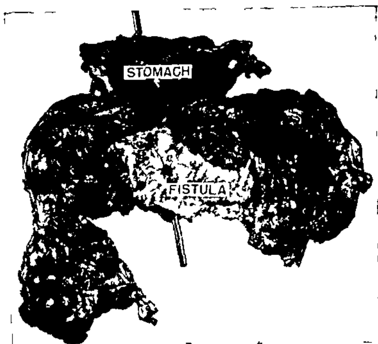


Fig 134 Gastrojejunocolic fistula

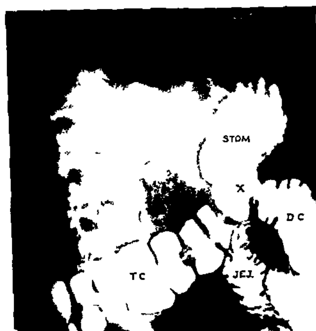


Fig 135 Roentgenogram taken after a barium enema showing a gastrojejunocolic fistula (Case 2) *T C* The transverse colon *D C* the descending colon and X the fistula

and may not be a true index of the amount of blood to replace Blood volume determinations would be of more value Since blood volume de terminations are not made in many hospitals however a working guide is to use about 40 cc of whole blood for every pound of body weight lost

The nutritional status of these patients is associated with severe avita minosis The avitaminosis is treated preoperatively with large doses of vitamin B complex and vitamins C and K We routinely give an ampule of solu B 500 mg of cevitamic acid and 72 mg of hyquinone daily

The ordinary methods of medically treating patients with marginal ulcer discussed elsewhere in this book are of no particular value once a gastro jejunocolic fistula has developed Morphine occasionally is of aid in treating the pain and diarrhea associated with the fistula but there is no medical therapy which offers a cure to these patients since its effects are the result of altered intestinal mechanics

We cannot overemphasize the importance of careful preoperative prepa ration of these seriously ill patients if a reasonable mortality and morbidity are to be expected after surgery

Postoperative Care

Once these patients have had a satisfactory first stage procedure divert ing the fecal stream away from the fistula their nutritive state improves greatly The diarrhea subsides almost immediately Food is readily ingested and absorption and digestive processes revert to normal A few days after operation the patients are placed on feeding regimens similar to those used for the treatment of marginal ulcer discussed elsewhere The patient s *nutrition rapidly improves and in a period varying from one month to* several months he is ready for the second stage procedure It is not uncom mon during this interval for the fistulous tract to close and the marginal ulceration to heal partially We believe however that all these patients should be subjected to resection of the stomach jejunum and colon if permanent satisfactory results are to be obtained Preparing the patient for the secondary stage and the care following resection are the same as the preoperative and postoperative care used with gastrectomy

CASE HISTORIES

Case 1 A man fifty four years of age first came to the Clinic in 1940 because of colitis From 1923 to 1929 he had suffered from epigastric pain and a diagnosis of duodenal ulcer was made *In January 1928* he had a mild hemorrhage *In October 1929 a gastro* enterostomy was performed For two years he was completely free from pain and distress From 1931 to 1934 he had several small hemorrhages From 1934 to 1937 usually twice a year October and May he passed small amounts of blood In 1936 he had from six to twenty bowel movements daily In 1937 a roentgenogram revealed a fistula between the jejunum and colon At the time of admission to the Lahey Clinic the frequency of bowel movements had increased and he had noticed a mass in the abdomen A diagnosis of gastrojejunocolic fistula was made In July 1940 an ileocolostomy was performed The terminal ileum was anastomosed to the descending colon Postoperatively he responded well His appetite returned and his bowels were moving only once a day at the time of discharge

The patient returned to the hospital three months later at which time the second stage procedure was performed consisting in removal of the right colon transverse colon stomach and jejunum (Fig 134) After this procedure he did well except for intestinal obstruction caused by adhesions This required another operation for lysis of adhesions Thereafter he did exceedingly well and has not had any trouble up to the present time

Case 2 A man aged forty eight years had the signs and symptoms of duodenal ulcer in 1931 In 1939 a subtotal gastrectomy with a posterior gastro enterostomy was per

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Chapter 58

PEPTIC ULCER IN MECKEL'S DIVERTICULUM

J ARNOLD BARGEN

INTRODUCTION

Since heterotopic mucous membrane is commonly found in Meckel's diverticulum (*see* Chap 1) peptic ulcers naturally would be expected to develop in this anomalous pouch of the intestine

Meckel's diverticulum is the most common congenital anomaly of the intestinal tract One of every fifty children is said to have it The next most common congenital anomaly namely hypertrophic pyloric stenosis affects *one out of every 200 All other congenital anomalies are said to occur in* the ratio of one in 1000 or more persons

There is a "rule of two" that is helpful in remembering some facts about the anatomy of Meckel's diverticulum It occurs in approximately 2 per cent of the population It occurs in two males to one female The diverticulum *is usually located about 2 feet proximal to the ileocecal valve Its length* averages about 2 inches Now of course great variations from this average rule have been occasionally reported Actually the diverticulum may be located anywhere between the pylorus and the ileocecal valve Its average length has varied from 2 5 to 12 5 cm and a Meckel diverticulum 56 cm in length has been reported

Ordinarily the wall of a Meckel diverticulum is made up of tissue like that of the adjoining ileum However the incidence of heterotopic tissue in Meckel's diverticulum is high These observations are of some interest when lesions such as ulcers of the diverticulum are under consideration

HISTORICAL ASPECTS

Carlson *in a study of 152 Meckel's diverticula found at necropsy at the* Mayo Clinic noted that 27 6 per cent contained heterotopic tissue In none of these cases did the Meckel diverticulum play any role in the cause of death The heterotopic tissue included stomach duodenum jejunum colon and pancreas and these occurred in seventeen different combinations In *one patient the Meckel diverticulum contained islets* of Langerhans cells During the period covered by Carlson's study eighty five patients who had Meckel's diverticulum came to operation at the Clinic In fifty five cases resection was performed and in forty seven of them it was felt that the diverticulum had some relation to the patients symptoms In the eight other cases it was *unquestionably responsible for* the patients symptoms Intestinal bleeding had occurred but in only five of these eight characteristic gastric mucosa was found

formed In 1944 severe diarrhea developed accompanied by mild abdominal pain and he lost weight Roentgen examination after a barium meal revealed no abnormalities A barium enema showed a gastrojejunocolic fistula (Fig 135) After preparation a first stage operation was performed on June 9 1944 anastomosing the terminal ileum to the descending colon The postoperative course was uneventful Three months later after his condition had improved considerably a second stage procedure was performed resecting the stomach jejunum and colon The patient made an uneventful recovery and was discharged from the hospital on his nineteenth postoperative day He did well until April 1947 at which time a jejunal marginal ulcer developed with hemorrhage A transthoracic vagotomy was performed

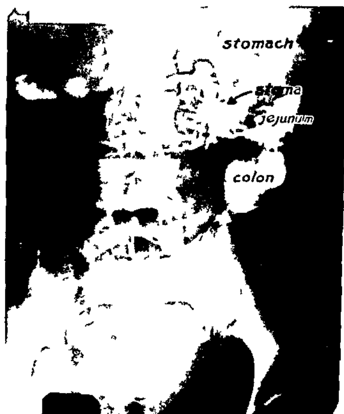


Fig 136 Roentgenogram taken after ingestion of a barium meal showing a gastrojejunocolic fistula

Case 3 A man forty three years of age had an operation in 1918 for a ruptured duodenal ulcer following ulcer symptoms of one year's duration In 1929 a gastro enterostomy was performed for recurrent symptoms of two years duration He had no symptoms until 1932 at which time diarrhea developed which continued until he was seen at the Clinic in 1938 In the interim he was treated for colitis A roentgenogram taken after a barium meal revealed a jejunal ulcer with a gastrojejunocolic fistula (Fig 136) Operation was performed and the distal ileum was anastomosed to the sigmoid He made an uneventful convalescence Two weeks later a second stage procedure was performed removing the stomach jejunum right colon and right half of the transverse colon After the second operation the patient made an uneventful recovery and was discharged from the hospital. Since that time he has been in excellent health

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have a typical ulcer syndrome The entire symptom complex of peptic ulcer may be mimicked However, the pain is usually periumbilical or to the right and below the umbilicus, rather than in the hypochondrium

Long protracted drainage from the umbilicus should call attention to the possible presence of Meckel's diverticulum The difficulties that usually call attention to Meckel's diverticulum are its inflammation perforation or hemorrhage These conditions are much more common in children than in adults

The symptoms due to Meckel's diverticulum are not unlike those produced by inflammation of the appendix vermiformis There may be associated fever right lower abdominal tenderness and all the other concomitant symptoms of appendicitis However the pain of Meckel's diverticulum is much more likely to be periumbilical The common distressing complication of Meckel's diverticulum is hemorrhage This may be an acute massive affair or there may be recurrent mild episodes of bleeding When children less than two years of age have bleeding from Meckel's diverticulum it is usually massive and it has been found to be so severe as to result in hemorrhagic shock

As indicated gastric mucosa jejunal duodenal or colonic mucosa and pancreatic tissue may be found in Meckel's diverticulum Gastric mucosa is by far the most frequently found of those mentioned and is the only type consistently associated with symptoms In children heterotopic gastric mucosa is the most frequent cause of symptoms ulcer is the most frequent complication resulting from this disorder The ulcer when it does occur is usually found in the intestinal mucosa adjacent to but not actually in the heterotopic gastric mucosa The ulcer is most often situated at the neck of the diverticulum or in the small intestine just beyond its neck However ulceration has been demonstrated in diverticula in which no trace of gastric mucosa was evident.

Thus the symptoms and signs indicating the presence of Meckel's diverticulum are those of its complications Although in some instances constriction of the diverticulum resulting from the outpouring of secretions from heterotopic gastric mucosa could well cause symptoms the most common symptom indicative of a disease condition in the diverticulum is the passage of fresh blood from the rectum

As a rule the blood which originates in an ulcer is not mixed with mucus a sign which differentiates the condition from acute intussusception Most patients have some type of abdominal pain which at times has its origin in the periumbilical region as a colic or a gnawing ache, similar in character to that of a duodenal ulcer and which may later migrate to the right lower abdominal quadrant The pain is not relieved by the ingestion of food and has no relationship to meals Often the onset of abdominal pain is followed by nausea and vomiting If the disease progresses without surgical intervention the signs and symptoms of perforation with diffusing peritonitis may appear In those instances in which the diverticulum causes intestinal obstruction the well known clinical picture of obstruction is presented In asymptomatic cases the diverticulum is usually found near the ileocecal valve whereas in cases presenting symptoms the diverticulum is more apt to be found 50 to 60 cm above the ileocecal valve

Few diagnostic aids are of any help in arriving at the finding of Meckel's diverticulum Theoretically roentgenologic examination should be of great

The difficulties of diagnosis are stressed by Owen and Finney[6] who found that each of twenty five patients who had Meckels diverticulum had one to three operations for rather bizarre but distressing abdominal symp toms and the Meckel diverticulum had been overlooked Eleven of the twenty five (44 per cent) had Meckels diverticulum with pathologic changes

Gastric mucosa is present in 16 per cent of all cases with Meckels di verticulum according to Schaetz[7] Cobb[3] reported a series of 100 cases of ulceration in Meckels diverticulum associated with the presence of gastric mucosa The ulcer usually occurred in the immediately adjacent ileal mu cosa that is near the base of the diverticulum Hemorrhage occurred in 72 per cent of Cobbs cases and perforation in 55 per cent 74 per cent of these patients were less than fifteen years of age No statistics are to be found illustrating the percentage of patients who have gastric mucosa in a diverticulum who also have peptic ulceration In addition to hemorrhage and ulceration a third complication is reported by Waugh and associates[8] These authors described two patients in whom the scarring resulting from the ulceration so reduced the lumen of the adjacent bowel that obstruc tion resulted

The mechanism of ulceration may be that discussed by Cobb namely acid secretion of the gastric mucosa of the diverticulum occurs at the same time as that of the stomach it therefore occurs at a time when the ileum lacks the protection of neutralizing food and secretions Thus favorable conditions are found for ulceration Acute perforation comparable to that in the stomach is found in Meckels diverticulum usually in the growing child less than eighteen years of age Perforation in the older age group is rare

In twelve of Owen and Finneys series[6] of sixteen cases of ulcer in the diverticulum gastric mucosa was associated but in the other four there was no evidence of heterotopia Ten of the ulcers were situated within the diverticulum three at the point of origin of the diverticulum and one in the ileum Those ulcers in which satisfactory sections were available were found at the junction of the two types of mucosa In no case was there more than one ulcer or perforation The point of perforation corresponded with the location of the ulcer The point of perforation was situated in the di verticulum in eleven cases in which perforation occurred was adjacent to the Meckel diverticulum in eight just at the level of fusion with the ileum in one and in the ileum in another

Mayo[4] noted that Meckels diverticulum is frequently suspected often looked for but seldom found Brown and Pemberton[1] pointed out that an unexplained anemia associated with a history of melena in a patient in whom no lesion was found by roentgenologic examination of the esophagus stomach duodenum or large intestine should arouse suspicion that there may be an ulcer in the ileum or Meckels diverticulum

DIAGNOSTIC SUGGESTIONS

It is generally agreed that a fourth of the patients who have Meckels diverticulum have symptoms of one kind or another Yet the diagnosis because of the location of the diverticulum in the small bowel is exceed ingly difficult. Patients may have distress in the low abdomen or they may

obstruction since the fluid state of the barium suspension is maintained in the absence of significant dehydrating action of the bowel Barium of course should not be given if closely knotted loops of the bowel are noted when the scout film is made

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Meckel s diverticulum includes consideration of all those conditions associated with melena obstruction and perforation Obviously then peptic ulcers of other portions of the gastro intestinal tract can usually be ruled out on the basis of history and roentgenologic findings When several massive hemorrhages have resulted from a duodenal ulcer the concentration of urea in the blood will increase soon after the hemor rhage This increase will occur rarely if ever after massive bleeding from an ulcer of Meckel s diverticulum Bleeding from the ulcers of the duo denum is rare among children less than two years of age whereas massive bleeding from the ulcers of Meckel s diverticula is relatively common In adults the problem of tumors of the small intestine must enter the differen tial diagnosis at all times The relative infrequency of neoplasms of the small intestine as compared to other regions of the alimentary canal is an aid in the differential diagnosis In a single decade when 600 malignant lesions of the esophagus 4500 of the stomach and 7200 of the large intestine were observed at the Mayo Clinic only 132 malignant tumors of the small intestine were found These included carcinomas lipomas sarcomas adenocarcinomas and hemangiomas

On first thought malignant lesions might be considered the most likely to cause bleeding like that seen in Meckel s diverticulum However as a matter of fact lipomas seem to be the most common of the bleeding lesions Although lipomas are frequently associated with no other symptoms the hemorrhages from other neoplasms of the small bowel are frequently as sociated with an abdominal tumor recurrent obstruction and at least pene tration of the wall of the bowel if not actual perforation The early diagnosis of any of these lesions depends on the careful taking of the his tory examination of the stools for blood and appropriate roentgenologic studies While Meckel s diverticulum may rarely be diagnosed as a result of roentgenography the latter is of the greatest importance in the differ ential study of this and other lesions of the small bowel Roentgenologic study of the small intestine should be carried out on all patients presenting symptoms of recurrent but not complete obstruction of the alimentary tract or bleeding when a satisfactory explanation is not found in the stomach esophagus or large intestine Furthermore it must be kept in mind that a peptic ulcer of Meckel s diverticulum may coexist with a jejunal or duo denal ulcer

The roentgenologic diagnosis of benign tumors of the small bowel in the absence of obstruction may be exceedingly difficult The demonstration of associated intussusception is the most frequent sign of benign neoplasms in this region The picture is that of a narrow barium filled tract lying within a loop of small intestine In some cases barium passes distally and may outline the intussusceptum lying within the lumen of the bowel

The amount of information which can be obtained from roentgenologic studies varies greatly in individual cases It is frequently not possible to

help The sac cannot be filled with barium since it is already filled but active peristalsis may be seen Since the advent of serial studies of the small bowel roentgenologists have on some occasions been able to show the presence of residual barium in Meckels diverticulum

Mighaccio and Begg demonstrated the shadow of Meckels diverticulum with some dilation of the bowel proximal to it. The condition was proved at operation to be due to a Meckel diverticulum but the roentgenologist considered it to be a retroperitoneal tumor encroaching on the lumen of the terminal ileum

Thus most authors on the subject have stressed the lack of value of the roentgenologic examination of the small intestine in making a diagnosis of Meckels diverticulum with or without complications However in more recent years evidence has accumulated that this method of examination is of greater importance than we thought in the past

The roentgenologic characteristics of Meckels diverticulum are similar to those of a diverticulum anywhere in the digestive tract Weber and Good[9] have reviewed the records of patients who were found to have Meckels diverticulum at operation at the Mayo Clinic from 1935 through 1946 Of 161 patients operated on thirty two had had preoperative roentgenologic examinations of the small intestine No roentgenologic evidence of abnormality was found in fifteen of thirty two patients In six of these the diverticula were incidental findings in the course of operations for other abdominal lesions in the others the diverticula were considered to be related to the patients abdominal symptoms and signs A definite roentgenologic diagnosis of Meckels diverticulum was made and confirmed at *operation in seven of the thirty two cases The roentgenologic diagnosis* of ulcerohyperplastic ileitis was made five times The diagnosis was verified at operation in every instance but Meckels diverticulum was also present an incidental finding in three of the cases involved in the ulcerohyperplastic process in one and with a linear ulcer on the mucosal surface in the other In one case the roentgenologic diagnosis of constricting neoplasm of the ileum was made At operation the lesion proved to be an ulcerative diverticulitis the inflammation extended to the ileum both orad and aborad to the diverticulum In another instance the roentgenologic examination revealed a mild and moderate degree of ileal obstruction but the nature of the obstructing process was not determined The diagnosis of obstruction was verified at operation and Meckels diverticulum proved to be responsible for it

It is probably true that a high percentage of Meckels diverticula will inevitably escape roentgenologic detection but given a patient who has known intestinal bleeding and in whom all other examinations are negative a suspicion of Meckels diverticulum should be entertained As Weber has pointed out negative findings on roentgenologic examination in cases of this kind may have a positive value

Sometimes too valuable information may be obtained from an ordinary scout film (preliminary survey) of the abdomen Entrance of barium into the Meckel diverticulum may have been delayed or the bowel may show signs of mild obstruction of the lower part of the ileum If there is gross obstruction of course a barium meal should never be given In contrast however to the situation in the large intestine barium may be safely introduced into the small intestine even in the presence of mild degrees of

obstruction since the fluid state of the barium suspension is maintained in the absence of significant dehydrating action of the bowel Barium of course should not be given if closely knotted loops of the bowel are noted when the scout film is made

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The amount of information which can be obtained from roentgenologic studies varies greatly in individual cases It is frequently not possible to

determine the type of a tumor of the small intestine Roentgenograms may show only a point of obstruction indicating the presence of a lesion but failing to yield evidence of the tumor Furthermore it is often difficult or impossible in a given case to distinguish with certainty a malignant neo plasm from regional enteritis Meckel s diverticulitis or other inflammatory type of lesion

When signs of inflammation are noted such other lesions as regional enteritis tuberculosis and sarcoidosis must be kept in mind of course How ever it is relatively rare for patients who have these lesions to have symp toms as mild and of as short a duration as those of Meckel s diverticulum It is thus rather unlikely that these conditions would be confused with those of Meckel s diverticulitis However rare as this situation may seem regional enteritis has been known to start in a most bizarre manner and to produce minimal symptoms the same holds true also of any type of small bowel disease Finally retroperitoneal lesions may cause angulation of the bowel and erosion through the lumen and thus simulate the signs and symptoms of a Meckel diverticulitis

TREATMENT

Medical Treatment Nothing of importance can be said about the medical treatment of Meckel s diverticulum Once the diagnosis is suspected or established surgical correction should be considered Of course when the patient is greatly depleted as from massive hemorrhage supportive meas ures including blood transfusions are essential It is probably well to say that the medical treatment involves the rehabilitation of the patient before operation

Surgical Treatment Uncomplicated Meckel s diverticulum rarely requires any surgical treatment except as it may be justifiable to remove it in the course of laparotomy for other purposes About a fourth of the patients who have Meckel s diverticulum present themselves because of symptoms of complications of the diverticulum at one time or another These compli cations which include perforating ulcers in Meckel s diverticulum melena obstruction and diverticulitis and occasionally intussusception and ma lignant changes may require surgical intervention

The technical procedure involved in excising Meckel s diverticulum may vary from simple ligation and excision to extensive resection of the small bowel when large diverticula are present Inversion of the diverticulum as is frequently practiced in appendectomy may be undesirable because of encroachment of the inverted tissue on the lumen of the small bowel If the base of the diverticulum is broad then excision with closure of the defect transversely with the long axis of the bowel has been practiced and finally removal of the diverticulum and resection of the adjacent bowel with anas tomosis of the bowel may be best At times too entero enterostomy around the narrowed bowel at the site of the diverticulectomy may be desirable

Preoperative and Postoperative Care If the patient has had hemorrhages from an ulcer of Meckel s diverticulum or recurrent attacks of diverticulitis with partial intestinal obstruction then it is wise to use the usual measures for rehabilitation of patients with intestinal disease before operation Pre operative administration of one of the antibiotics particularly aureomycin blood transfusions and other measures of rehabilitation are always worth

while A diet which provides a minimal residue for a few days before operation is of help A sample of such a diet is as follows

DIETARY PATTERN AND SAMPLE MENU FOR DIET WITH MINIMAL RESIDUE

Breakfast	
Orange juice	½ glass
Refined cereal (farina)	½ cup (cooked)
Soft cooked eggs	2
White toast	1 slice
Butter	1 square
Coffee	1 cup
Cream	⅓ cup
Sugar	½ tablespoon
Jelly	1 *teaspoon*
Dinner	
Broth	½ cup
Roast beef	3 oz
Gravy	¼ cup
Buttered noodles	½ *cup*
Vanilla ice cream	⅓ *cup*
White toast	1 slice
Butter	1 square
Jelly	1 teaspoon
Tea	1 cup
Sugar	½ *tablespoon*
Supper	
Cold sliced ham	[illegible] oz
Poached egg	1
Steamed rice	½ cup (cooked)
Chocolate pudding	½ cup
Cream	¼ cup
White toast	1 slice
Butter	1 square
Jelly	1 teaspoon
Tea	1 cup
Sugar	½ *tablespoon*
Between Meal Feedings	
Fruit juice with sugar at 10 A M	1 glass
Baked custard or gelatin dessert at 3 P M	½ cup

Colonic irrigations for a few days before operation also may be helpful These measures are particularly important in providing a relatively empty large intestine

REPORT OF CASE

A widow aged forty two years came to the Mayo Clinic on February 3 1947 because of periodic episodes of epigastric pain and vomiting She stated that she had last been perfectly well four years before coming to the Clinic At that time she had begun having nausea, vomiting and constipation periodically but not until two years prior to admission was she hospitalized for so-called acute indigestion She complained of cramping in the upper part of the abdomen nausea and vomiting She had been hospitalized for six weeks A diagnosis of tumors in the lower part of the abdomen was made Pains were cramplike and extended through to the back Thereafter the attacks were recurrent she would be free of them and would feel well for two or three months and then she would have to stop working because of an episode of distress

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tumor and ileo-ileostomy were performed The lesion was an intussuscepted Meckel diverticulum with heterotopic pancreatic tissue and heterotopic gastric and duodenal mucosa with ulceration There was marked thickening of the wall and dilatation of lumen of the ileum proximal to the lesion which was 8 cm from the distal end of the specimen.

This case illustrates well the difficulties encountered in making a diagnosis of peptic ulcer in Meckel's diverticulum

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In the spring of 1946 she had been hospitalized a second time for a week. In October 1946 roentgenologic examinations were made the results of which were indeterminate. Later that month vomiting began again and she was hospitalized for the third time At this time the administration of parenteral fluids was necessary and she had some swelling of the legs The following month she had a supravaginal hysterectomy bilateral salpingectomy and left oophorectomy Since then there had been intensification of the upper abdominal cramping and frequent vomiting unless she received hypodermic injections of sedatives At times she would vomit as much as a quart (1000 cc) of bile-stained fluid She had lost about 36 pounds (16 3 kg) in the three months prior to admission at the Clinic and her weight at that time was 109 pounds (49 4 kg)



Fig 137 Entero t t nc intus usceptı n and inversion of Meckel s diverticulum The pathologist found heterotopic gastric and duodenal mucosa with ulceration

Physical examination at the Clinic disclosed ballooning of the intestinal loops low in the abdomen and evidence of colicky cramplike pains On admission the value for hemoglobin was 10 6 gm per 100 cc of blood Erythrocytes numbered 4 030 000 and leukocytes 7400 per cubic millimeter The urine was clear The sedimentation rate was 20 mm the first hour by the Westergren method The value for blood urea was 22 mg per 100 cc The blood chlorides measured 594 mg per 100 cc The carbon dioxide combining power of plasma was 61 7 volumes per cent On proctoscopic examination the rectal lining appeared normal for 24 cm Roentgenologic examination of the colon showed it to be free of any intrinsic lesion throughout its extent There was some evidence of distention of the coils of small intestine in the right side of the abdomen Because of her recent operation and the fact that complete relief of the obstructive features was obtained after suitable measures of decompression roentgenologic studies of the small bowel were carried out cautiously They disclosed a polypoid lesion about 3 cm in diameter in a loop of ileum in the left lower quadrant of the abdomen The tumor had caused intussusception of several inches of bowel (Fig 137)

Surgical exploration was advised and resection of the portion of the ileum bearing the

Section VIII

Complications of Gastroduodenal Ulcer

Chapter 59

GASTRO INTESTINAL HEMORRHAGE

LEON SCHIFF AND NATHAN SHAPIRO

In this chapter consideration of hemorrhage will be confined to that arising in the upper reaches of the digestive tract Bleeding from hemorrhoids is easily recognizable and bleeding due to lesions of the colon should be readily detectable by rectal proctosigmoidoscopic or x ray examination It is well to bear in mind that the character of the stools does not necessarily differentiate a high site" from a "low" one Thus in the presence of intestinal hypermotility blood introduced orally or intragastrically may appear bright red in the stools [47] It is well to remember that tarry stools unaccompanied by hematemesis may occur in lesions of the lower esophagus or stomach and that they do not necessarily indicate a bleeding point beyond the pylorus We have never seen tarry stools arise from a lesion distal to the ileocecal valve although this is said to occur rarely and has been produced experimentally [24] Furthermore the clinician may have recourse to the blood urea nitrogen to help determine the site of hemorrhage since the blood urea nitrogen is not elevated when bleeding into the intestinal tract arises from the large bowel

BLEEDING PEPTIC ULCER

It is generally agreed that bleeding peptic ulcer is the most common cause of hematemesis and melena Causes of bleeding from the upper digestive tract as seen at the Cincinnati General Hospital in an experience covering a ten year period are listed in Figure 138

A typical "ulcer syndrome" preceding hematemesis or melena is almost indicative of bleeding peptic ulcer if one can exclude gastric carcinoma erosive gastritis and exceptionally hiatal hernia In a fair proportion of patients with peptic ulcer there is no characteristic "ulcer syndrome" preceding hemorrhage In thirty four of 339 proved cases of bleeding peptic ulcer there was no history of any digestive distress prior to the hemorrhage while in seventy the distress was atypical [41]

Ulcers situated on the posterior wall of the duodenum are most apt to bleed because the arterial supply enters from behind and the bleeding is usually due to erosion of an artery lying in the base of the ulcer Alsted[1] believes that associated gastritis is sometimes the source of hemorrhage Recently attention has been called to the frequency of postbulbar ulcers which are said to be more prone to bleed than ulcers in the duodenal cap [2] Bleeding is also said to be more frequent in marginal ulcers[5, 15] (Figs 139 and 140)

Of clinical interest and importance is the frequent disappearance of ulcer pain after hemorrhage The mechanism of this phenomenon is not known Lack of gastric tone [8] the presence of blood in the crater covering

cirrhosis congestive splenomegaly (Banti s syndrome) gastric neoplasm and blood dyscrasias It is well to remember that the spleen may contract



Fig 139 Two jejunal ulcers with recent history of bleeding

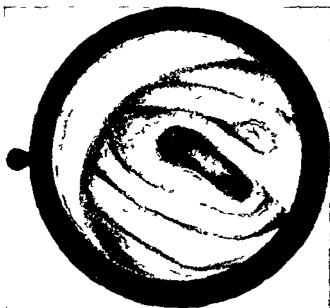


Fig 140 Acute marginal ulcers as seen at gastroscopy

soon after hemorrhage thus temporarily concealing its previous enlarge ment

the pain nerve ends and hindering their excitation by hydrochloric acid[7] and the neutralizing effect of blood (in the stomach) on gastric acidity[43] have been suggested

One frequently obtains from patients with bleeding ulcer a history of fainting in the bathroom The loss of consciousness in these circumstances is probably explained on the basis of the observations of Wallace and Sharpey Schafer[44] who reported syncope following return to the upright

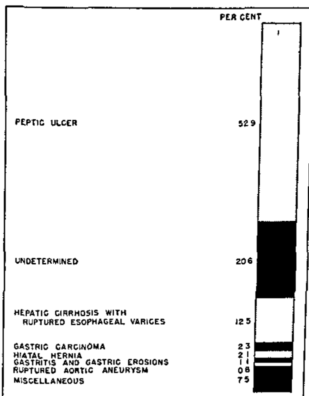


Fig 138 Causes of bleeding from the upper digestive tract (Reproduced from C M MacBryde Signs and Symptoms Their Clinical Interpretation with the permission of J B Lippincott Company)

position after the rapid removal of 900 to 1150 cc of blood in control subjects

In cases of mild hemorrhage there may be little more than hematemesis or melena In more severe cases weakness dizziness faintness thirst syn cope or shock may occur and in these circumstances the history obtained from the patient is frequently unreliable

At times bleeding occurs after acute emotional distress[11 18 30] The en gorging effect on the gastric mucosa of sustained resentment, anxiety and frustration may play a role in pathogenesis of ulceration[48] One patient with a known duodenal ulcer was symptom free for two years and suffered hematemesis two days after the drowning of a son another bled two days after his wife left home

Physical examination is usually of no help in the diagnosis of bleeding peptic ulcer except to exclude other causes of hemorrhage such as hepatic

emergency operation is contemplated) and that it may occasionally reveal evidence of ulcer not detectable on x ray examination repeated ten days to two weeks after the hemorrhage has ceased The procedure proved positive in 119 of 162 cases of bleeding peptic ulcer and in an additional seven cases revealed one of two coexisting lesions either of which may have been responsible for hemorrhage [41] It may reveal unsuspected esophageal varices hiatal hernia or gastric neoplasm If early roentgen examination fails to reveal an ulcer study at ten to fourteen days of a more definitive nature with compression may at times reveal the lesion

Gastroscopy carried out within three to ten days after hemorrhage as advocated by Jones[30] (and corroborated by our experience) may fre



Fig 143 Esophageal varices demonstrated by the Hampton technic

quently reveal ulceration not detectable on subsequent x ray examination In one of our patients gastroscopy on the third day following hematemesis revealed an ulcer which was not demonstrable on subsequent x ray examination (Fig 144)

It may be difficult to differentiate malignant gastric ulcer from a benign lesion at the time the patient is first seen It may be necessary to resort to the usual criteria of effect of therapy on the lesion itself as determined by symptomatic improvement x ray and gastroscopic findings and at times even to operation We have seen bleeding from a malignant gastric ulcer in a patient who twenty five years before had had a pyloroplasty for duodenal ulcer Our diagnosis in this case prior to operation which had to be invoked in order to stop the bleeding was benign gastric ulcer

Carcinoma of the ampulla of Vater may simulate bleeding duodenal ulcer One of our patients had pyloric obstruction and hematemesis x ray examination showed a nichelike configuration in the second portion of the

At the Cincinnati General Hospital roentgen examination of the patient soon after the occurrence of hemorrhage as recommended by Hampton [1]



Fig 141 Gastric ulcer visualized with the Hampton technic

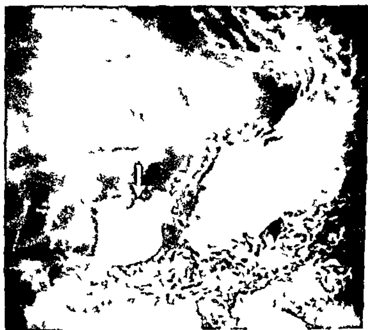


Fig 142 Duodenal ulcer visualized by the Hampton technic

has been carried out *with much success* (Figs 141 142 and 143) We are *convinced* that the procedure is safe and of great help (particularly when

duodenum (Fig 145) which was interpreted as postbulbar ulcer At opera tion it was found that the ulceration was due to a carcinoma of the ampulla

Not infrequently the clinician may find himself confronted with two lesions either of which may account for hemorrhage For example it is not unusual to encounter a coexisting hiatus hernia and gastric or duodenal ulcer or coexisting peptic ulcer and esophageal varices In one such case in which bleeding continued it was necessary to resort to esophagoscopy in order to rule out bleeding varices In this instance laparotomy was per formed immediately after the esophagoscopy and revealed a bleeding duodenal ulcer In dealing with hematemesis in the face of coexisting esophageal and gastroduodenal lesions one may have recourse to the Ein horn string test,[14] although our own experience in this connection is virtu ally nil The string test may occasionally suggest a bleeding site in the lower esophagus stomach or duodenal bulb when x ray and other studies are negative

Occasionally a carcinoma of the body of the pancreas eroding the duo denum or stomach may result in hemorrhage simulating bleeding peptic ulcer In one such case the patient was subjected to emergency laparotomy Similarly a recent case of ulcerated benign gastric tumor with massive hemorrhage was subjected to emergency operation with a preoperative diagnosis of bleeding ulcer It is evident therefore that at times the cause of hematemesis and melena may be determined only at operation carried out to stop bleeding clinically attributed to peptic ulcer Occasionally the correct diagnosis may be made only at necropsy and sometimes even autopsy may fail to disclose the cause

HEMORRHAGE OF UNDETERMINED CAUSE

In about one fifth of our cases of hemorrhage from the upper digestive tract the cause of the bleeding is not proved either roentgenologically or gastroscopically White and Chalmers[47] reported only 9 5 per cent of unde termined causes among 400 patients They used the Hampton technic in only twenty five of their patients and give no statement regarding the frequency of gastroscopic examination In many of the "undetermined cases" there is an "ulcer syndrome" present and the bleeding is probably due to ulcer but roentgen proof is lacking or gastroscopic examination done ten to fourteen days after hemorrhage proved negative We have made it a practice to include such cases among the undetermined causes

It is probable that if the Hampton technic were used routinely and gas troscopy carried out regularly three to ten days after hematemesis the incidence of "undetermined causes" would be appreciably reduced Jones [9] performed gastroscopy in 116 of 217 cases of bleeding ulcer in which the diagnosis of the cause of bleeding was not made on clinical and radiologic examination and found a gastric ulcer in sixty five instances Olsen and Moersch[33] have recently stressed the role of endoscopy in the diagnosis of upper gastro intestinal hemorrhage of obscure origin

CIRRHOSIS OF THE LIVER

In hepatic cirrhosis hematemesis is usually due to a ruptured varix in the lower end of the esophagus The rupture may occur spontaneously or

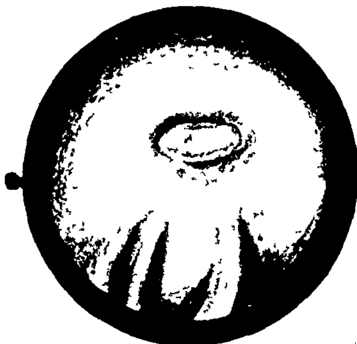


Fig 144 Photograph of drawing of superficial gastric ulcer made at gastroscopy 3 days after massive hematemesis (Reproduced from C M MacBryde Signs and Symptoms Their Clinical Interpretation with the permission of J B Lippincott Company)



Fig 145 Ulcer niche in second portion of duodenum due to carcinoma of ampulla of Vater

rhage is more apt to occur from malignant ulcers Not infrequently there may be no hematemesis but only melena

It is well known that gastric carcinoma is more commonly seen in males forty years of age or older Anorexia loss of weight or mild or vague abdominal distress is often present The history may be that of a typical peptic ulcer syndrome" which may have even improved temporarily under inadequate ulcer management As has been repeatedly emphasized a suspicion of carcinoma should be entertained if persistent digestive symptoms regardless of their triviality occur in a middle aged person previously free of digestive distress

Physical examination may be entirely unrevealing in the absence of metastatic spread Attention should be given to the presence of enlarged nodes in the left supraclavicular fossa an enlarged liver an epigastric mass or a Blumer s shelf

The presence of a persistent achlorhydria in a patient with recent hematemesis and melena should lead to a suspicion of gastric carcinoma

Roentgenograms are the most valuable single agent in the diagnosis of gastric carcinoma In skillful hands they reveal the presence of a lesion in over 90 per cent of the cases the most characteristic change is the constant filling defect in the involved portion of the stomach Occasionally the lesion may be recognized with the Hampton technic Gastroscopy is also of value in diagnosis[3]

HIATUS HERNIA

Bleeding in cases of hiatal hernia may be due to congestion of the blood vessels in the herniated portion of the stomach to gastritis or ulceration There may be ulceration of the esophagogastric junction (Fig 146) or hernial pouch or a gastric ulcer may be found adjacent to the hernia

Patients with hiatal hernia are usually in the later decades of life and are frequently overweight The history may contain no reference whatever to disorders of the stomach or the gastric symptoms may be secondary to gallstones[6] There may be a history of repeated attacks of anemia heart burn and vomiting[6] Jones[9] has noted the frequency of substernal or epigastric pain induced by exertion emotional tension excessive eating or lying down and relieved by the administration of atropine and less often by belching or administration of nitroglycerin He found heartburn to be rather characteristic and regurgitation more frequent than vomiting in patients with small hernias

Hurst[3] noted the occurrence of pain or the feeling of pressure under the xiphisternum or a little to the left and occasionally in the back, immediately after swallowing The radiation of the pain to the heart and left arm simulating angina pectoris has been emphasized by von Bergmann Hurst and Jones[5] [9] The attacks of distress are mostly nocturnal and may disappear on assuming the sitting position Intermittent dysphagia may be experienced[9] [5] Intermittent herniation and distress may result from increase in the intra abdominal pressure produced by bending forward as in putting on one s shoes or straining at stool

Endoscopy and roentgen examination are of great help in diagnosis It is important that the roentgenologist exercise particular effort to demon

may follow excessive physical activity uncontrolled vomiting and coughing[42] The cause of the rupture is not entirely known but is believed in part attributable to the relatively high local venous pressure Whipple[46] has mentioned the possible role of trauma associated with the frequent contractions of the esophagus and the pressure and passage of boluses of food *Peptic ulceration of the esophageal mucosa overlying the varices as the* result of reflux of acid gastric contents into the esophagus has been suggested by Wangensteen[45] Occasionally the bleeding in cases of cirrhosis may be due to hypoprothrombinemia thrombocytopenia or ulcerative esophagitis or gastritis

The presence of cirrhosis may be suspected in a patient with chronic alcoholism or with a history of a diet deficient in meat and dairy products *Anorexia morning nausea vomiting flatulence and not infrequently diar*rhea of some standing may precede the hematemesis The presence of jaundice ascites edema vascular spiders distended veins on the abdomen and chest palmar erythema a palpable liver or spleen may prove helpful in clinical diagnosis

Laboratory tests may reveal a positive cephalin cholesterol flocculation test increased thymol and/or zinc sulfate turbidity increase in serum *bilirubin retention of bromsulfalein and reduction of serum albumin* White and Chalmers[47] and Zamcheck and associates[49] have emphasized the uniform presence of abnormal bromsulfalein retention in cases of cirrhosis with hematemesis particularly during shock While abnormal dye retention may occasionally be encountered in other bleeding lesions "at the time of shock or soon after these authors believe that a normal bromsulfalein retention soon after a severe hemorrhage practically excludes *esophageal varices associated with hepatic cirrhosis as the cause of the* bleeding

Needle biopsy of the liver has been extremely helpful in the diagnosis of hepatic cirrhosis[36] but is best carried out after recovery from hemorrhage It is helpful in distinguishing nutritional from postnecrotic cirrhosis It may occasionally be negative in postnecrotic cirrhosis because of the uneven distribution of the lesion

The demonstration of esophageal varices on x ray examination (see Fig 143) or esophagoscopy may prove extremely helpful in diagnosis Shatzki[4] *advises that the roentgen examination for varices* be made with the patient in the horizontal position since varices become smaller in the erect position He uses a suspension of equal parts of barium and water and advises coating the inner surface of the esophagus with only a thin layer of barium since filling the organ with a large amount of opaque medium will obliterate the protruding vessels He advises that films should be taken in several projections after slight inspiration since during this phase the lower end of the esophagus is stretched slightly

CARCINOMA OF THE STOMACH

Bleeding in gastric carcinoma is usually due to ulceration of the tumor or necrosis and sloughing of papillary growths The bleeding usually takes the form of oozing or seepage *but occasionally a medium sized or large* artery may be eroded resulting in massive hematemesis Massive hemor

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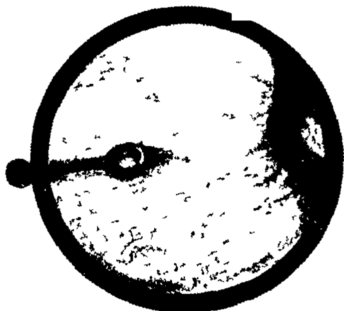


Fig 147 Photograph of a drawing of a bleeding mucosal erosion seen at gastroscopy There was associated hypertrophic gastritis evidenced by the polygonal pattern of the nearby mucosa (Reproduced from C M MacBryde Signs and Symptoms Their Clinical Interpretation with the permission of J B Lippincott Company)



Fig 148 Photograph of drawing of hypertrophic gastritis as seen at gastroscopy

strate the lesion by examining the patient in both the supine and prone positions with forceful increase in intra abdominal pressure The hernia may be visible on one examination and not on another so that in doubtful instances the roentgen examination should be repeated Occasionally the proof that the hiatal hernia was the cause of hemorrhage may be pre



Fig 146 Ulcer at esophagogastric junction in hiatal hernia

sumptive and based on the failure of hemorrhage to recur after repair of the hernia

GASTRITIS

Gastritis has long been recognized as a cause of varying degree of digestive tract hemorrhage [4 16 2] In a series of forty two cases of hemor rhage from gastritis Benedict reported the bleeding to be mild in seven moderate in fourteen and severe in twenty one The bleeding in chronic gastritis usually arises in erosions of the mucous membrane (Fig 147) In some cases there may be oozing from the mucosa without demonstrable erosion [38 39] Schindler believes that most of the profuse hemorrhages from gastritis occur in the chronic hypertrophic form (Fig 148)

There is no characteristic history in patients with chronic gastritis In some the story may be that of an ulcer syndrome The x ray examination is of relatively little value in the diagnosis which is almost entirely based on gastroscopic examination [39]

AORTIC ANEURYSM RUPTURING INTO THE ESOPHAGUS

The patient is usually a male and there is frequently a history of sub sternal pain dyspnea and cough Shock is usually present A tracheal tug

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may be detected While roentgen examination of the chest is of inestimable value in one of our patients in whom the diagnosis was proved at autopsy the aneurysm was not demonstrable on an anteroposterior view of the chest It might have been detected on fluoroscopy

MISCELLANEOUS CAUSES

In our experience miscellaneous causes of hematemesis and melena have comprised the following disorders arranged somewhat in their order of frequency blood dyscrasias erosive esophagitis and/or erosive gastritis associated with liver disease mesenteric thrombosis carcinoma of the esophagus malignant tumors eroding into the gastro intestinal tract—usually carcinoma of the pancreas—ulcerative esophagitis Banti s syndrome (extrahepatic portal block) benign tumor of the stomach

Some of the rarer causes of hemorrhage from the upper gastro intestinal tract which we have encountered in our series of cases are acute esophagitis with pancreatic necrosis chronic relapsing pancreatitis cholecysto duodenal fistula Curling s ulcer erosion of the aorta due to periaortitis gastric varices lymphosarcoma of the stomach prolapsed gastric mucosa ulcerated heterotopic gastric tissue

Others have reported hemorrhage from localized arteriosclerosis of gastric vessels [17] hereditary telangiectasia [0 31] tumors of the small intestine [40] and rupture of aneurysm of the hepatic[19] or splenic artery [3] Hematemesis and melena have also been ascribed to aspirin in sensitive subjects Slight to intense hyperemia and hemorrhage have been reported on gastroscopic examination after ingestion of aspirin [3 10 1 13 6 7]

Heuer [3] reported an interesting case in which the pathologist failed to find any erosion of the mucosa of the duodenum or stomach but was able to demonstrate a small ruptured aneurysm concealed by overlying mucosal folds when he injected the gastric artery with saline solution from a pressure bottle This experience may possibly shed light on the occasional case of hematemesis and melena which is not diagnosed even after necropsy

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hematocrit may be entirely normal But as the body endeavors to increase the circulating blood volume fluid is withdrawn from tissues into the blood stream hemodilution occurs and finally over a period of hours anemia becomes apparent in laboratory examinations (Fig 149)

The majority of ulcers will stop bleeding spontaneously as a result of the mechanisms indicated in a previous paragraph If these natural defenses fail for some reason (for example arteriosclerosis or erosion of a main artery) there will be continuing hemorrhage or recurrent hemorhage with persistent shock these patients face the dangers of anoxemia of vital organs When the blood pressure falls below a certain critical level, the vasocon

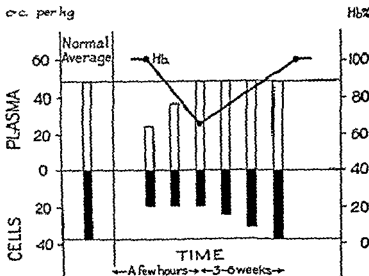


Fig 149 Diagram illustrating reduced blood volume with normal hemoglobin shortly after a single severe hemorrhage As hemodilution restores plasma volume the extent of hemoglobin reduction becomes apparent over a period of hours Restoration of cell volume requires weeks (From Bockus Gastro-enterology after Bennett, Dow and Wright)

strictor center suffering from impaired blood supply becomes weakened and loses its tone resulting in further decline of blood pressure[3] Cerebral anoxemia will be indicated by mental confusion of any degree—for example impaired memory for recent events Prolonged shock will cause prerenal azotemia with lowered urinary excretion and elevated blood urea nitrogen The occurrence of sudden anemia in a patient with coronary artery disease may precipitate infarction Wood[32] suggested that a fresh erosion of devitalized tissue around an ulcer may cause recurrent hemorrhage

Blood volume determinations represent the most accurate index of the severity of the hemorrhage[4] but such studies are not generally available *

* Gregersen [3] described a practical method for the determination of blood volume with the dye T 1824 (Evans blue) By using a standard amount of dye solution of known concentration the plasma concentration of the dye is measured with a portable Decade photometer using a single sample of blood drawn ten minutes after dye injection. By reference to a chart the total plasma volume is obtained directly from the photometer reading The total blood volume is then calculated from the plasma volume and the hematocrit With

(Footnote continued on p 638)

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Chapter 60

TREATMENT OF HEMORRHAGE FROM GASTRODUODENAL ULCER

H MARVIN POLLARD AND ARNOLD WOLLUM

PHYSIOLOGIC CONSIDERATIONS

Hemorrhage from peptic ulcer may result from an erosion of a sizeable artery or vein such as the right or left gastric arteries the gastroduodenal or pancreaticoduodenal vessels More commonly it probably represents bleeding from vascular granulation tissue at the base of the ulcer or erosion of a small but congested vessel in the inflamed area surrounding the ulcer The hemorrhage may be massive regardless of the size of the vessel involved If a bleeding artery is sclerotic or if the vessel is imbedded in the firm scar tissue of chronic ulceration bleeding is apt to be prolonged *and even fatal because of inability of the vessels to contract or to constrict* the lumen

According to Best and Taylor[6] when a sudden large hemorrhage occurs *there is usually a fall in blood pressure as a result of sudden reduction in* the circulating blood volume Unless the blood loss is rapid and amounts to more than 10 per cent of the total blood volume compensatory mechanisms will easily maintain the blood pressure In more severe bleeding the initial fall in blood pressure if not too great is of benefit in preventing further hemorrhage Blood clots more rapidly after a severe hemorrhage and this plus the low blood pressure is usually effective in sealing the leak even in large vessels In arteries retraction of the middle fibromuscular coat and curling of the endothelial lining are further defenses against continued bleeding

Soon after hemorrhage begins the pulse rate rises and vascular reflexes bring about a redistribution of the remaining blood volume in order to maintain vital areas Vasoconstriction in the skin mucous membranes intestines and other less essential areas results in the clinical picture of shock At this point, blood studies such as the hemoglobin red blood count, and

Continuation of pain following a severe hemorrhage usually means lack of ulcer healing[7] and may herald continued bleeding The mortality rates are higher for cases with massive hematemesis than for those with melena alone[21] hematemesis often being an indication of acute copious hemorrhage Elevation of the blood urea nitrogen is considered ominous if the level is persistently high continues to rise or if it reaches 100 mg per cent [7] Severe hemorrhage is of course always accompanied by higher mortality rates regardless of variations in the method of therapy a severe hemorrhage is indicated by a hemoglobin below 50 per cent (8 gm) or a red blood count below 2 5 million persistent continuing hemorrhage or repeated hemorrhage or persistent shock Patients who cease bleeding soon after admission to the hospital and who have a recurrent massive hemorrhage after a day or so show a sharp increase in mortality [5] Mortality rates will always be higher in patients with coexisting disease or complications hypertension arteriosclerosis intercurrent infections ulcer perforation or pyloric obstruction and so forth Ulcers which bleed in the patient already on a full medical ulcer regimen often carry a poor prognosis [16] The over all mortality of all peptic ulcers with manifest hemorrhage is estimated by Ivy and associates at around 7 5 per cent

BACKGROUND OF PRESENT FORM OF THERAPY

Prompt Feeding Before 1931 the routine medical management of bleeding ulcer comprised bed rest nothing by mouth morphine and an ice bag to the epigastrium After three or four days the patient was started on a thin gruel diet In 1938 Miller and Elsom [3] collected 5843 cases in the literature mostly treated by the starvation regimen yielding a mortality rate of 8 7 per cent (9 1 per cent if prompt feeding cases included were omitted)

In 1931 Meulengracht of Denmark observed that sometimes patients with protracted hemorrhage stopped bleeding when they were given food and that often ambulant patients recovered from severe melena without making any particular change in their ordinary diet He questioned the desirability of starving a patient at a time when he presumably needs food for the processes of healing and regeneration He also felt that the empty stomach was more active than the full stomach and that the combination of an empty stomach with free hydrochloric acid was not good ulcer treatment He therefore began treating his patients with prompt feeding of a bland diet of five meals a day Meulengracht felt that this program resulted in more rapid recovery in all respects a more contented patient and a lowered mortality rate [0, 21] In 1947 Meulengracht reported the results of 1031 consecutive cases of bleeding peptic ulcer so treated [2] The gross mortality rate was 2 5 per cent but by excluding deaths from causes other than bleeding as well as excluding patients who died within twenty four hours ("before they had received the treatment") the net mortality rate was 1 5 per cent

Meulengracht s statistics have been the subject of some controversy It has been pointed out that hospitalization is easier under the socialized medicine of Denmark than in the United States and that therefore Meulengracht s series probably contains many mild hemorrhages Indeed x ray proof of ulcer was lacking in many of his cases suggesting hemorrhage

The hemoglobin red blood count and hematocrit determinations are valuable but they tend to lag behind the clinical course of the patient The best immediate indications of the severity of a continuing hemorrhage are the clinical findings—falling blood pressure rapid pulse and other manifestations of shock Loss of over 30 per cent of the total blood volume from brisk hemorrhage usually causes death unless transfusions are given

Azotemia in association with gastroduodenal hemorrhage may be due to a number of factors according to various authorities [7] Among these are (1) elevation of the blood urea nitrogen as a result of absorption of digested hemoglobin and other blood proteins from the digestive tract (2) shock or dehydration with decreased renal clearance of urea and (3) increased catabolism of body proteins as a result of starvation or an "alarm" stimulus Of these factors the absorption of digested blood is probably the most common 1 liter of blood contains 140 gm of protein or about twice the daily normal protein intake A persistently elevated or rising blood urea nitrogen sometimes indicates a poor prognosis usually being an index of *continued bleeding or shock However, this must not be looked on as an* infallible index since deaths from hemorrhage have occurred in patients with relatively normal blood urea nitrogen values

PROGNOSTIC FACTORS

Statistical studies of bleeding ulcer in the past have indicated increased mortality expectancy in certain patients The collected statistics analyzed by Ivy Grossman and Bachrach[17] are particularly informative in this respect The mortality rate for men with peptic ulcer hemorrhage is slightly higher than for women the death rate being 10 6 per cent for men and 8 3 per cent for women The significance of age in ulcer hemorrhage is clearly indicated by a mortality rate of 4 3 per cent for patients below the age of forty and 12 6 per cent above this age The mortality rate rises steadily with advancing age This is probably a reflection of the higher incidence of arteriosclerosis and other complicating disease in the older age groups Arteriosclerosis is important in mortality not only because the arteriosclerotic blood vessel may fail to collapse and thereby prolong bleeding but also because the combination of anemia and arteriosclerosis of coronary and cerebral vessels may precipitate deaths from vascular accidents The mortality from bleeding gastric ulcer tends to be approximately 17 per cent that of duodenal ulcer 9 per cent The higher mortality in gastric ulcer is attributed to the frequent erosion of the right or left gastric arteries Hemorrhage from anastomotic ulcer causes a mortality of about 6 per cent Chronic peptic ulcer is found in 66 per cent of fatal hemorrhages acute ulcer in 28 per cent

Most deaths from ulcer hemorrhage occur during a first hemorrhage (78 per cent of all deaths according to Blackford and Williams[8]) The reason for this is not clear Absence of previous ulcer symptoms gives a better prognosis in ulcer hemorrhage than if there is such a history[8] because a long history of ulcer symptoms is more likely to mean a deep chronic ulcer

this technic the average total blood volume in normal men was found to be 85 1 ml per kilogram [24] This technic has been successfully and enthusiastically used by Rudman and Stewart who conclude that the T 1824 dye technic is a convenient guide to the severity of hemorrhage especially in the early hours after the onset of bleeding [25]

cases) Undoubtedly the next few years will see increasing trial of early surgery in patients with severe hemorrhage particularly in hospitals with specially trained teams equipped for handling these cases on an emergency basis Facilities in such a set up must include adequate laboratory services liberal blood bank supplies as well as expert professional care At present the results of the *average* medical program are statistically superior to the results of *average* surgical therapy in ulcer hemorrhage For this reason the initial treatment of gastroduodenal hemorrhage should be medical

Transfusions Many conflicting statements have appeared in the medical literature regarding the value and dangers of blood transfusion in bleeding peptic ulcer Jones[18] lists the dangers of transfusion as reactions serum transmitted hepatitis Rh antibody difficulties and overloading the circulation. The chief roles of blood transfusion include prevention of death from exsanguination alleviation of hemorrhagic shock prevention of damage to vital organs by anoxemia maintenance of the hemoglobin at a sufficiently safe level so that a recurrent hemorrhage will not threaten life and preservation of the patient in suitable condition for possible surgical intervention

Approximately two thirds of all manifest hemorrhage cases will be classed as mild to moderate hemorrhage (*i e* blood *hemoglobin stabilized above 8 gm* or 50 *per cent red blood cell count above 2.5 million and without persistent shock or recurrent hemorrhage*) *Most such patients cease bleeding quickly and spontaneously and do not require transfusions* In patients with *more severe hemorrhage* transfusions must not be withheld for long periods or the patient s life will be jeopardized, particularly if he is a potential surgical candidate

Usually blood is given in citrated form by slow intravenous drip (500 cc. over a period of several hours) The amount and rate of administration must be sufficient to counteract shock and, if possible to restore the hemoglobin to a relatively normal level In rare cases of rapid severe hemorrhage it is sometimes necessary to give blood simultaneously into two veins at one time in order to combat shock Intra arterial transfusion may have a place in rare cases of rapid massive hemorrhage in which the circulation cannot be restored in any other way

RECOMMENDED PLAN OF THERAPY

This *includes* (1) *hospitalization*, (2) *bed rest*, (3) *a prompt feeding program*, (4) *medications for control of gastric acidity to speed healing of the ulcer* (5) *adequate utilization of blood transfusions and control of dehydration and* (6) *consideration of early operation in patients who do* not respond to these measures

General Measures On admission the patient is placed at bed rest, a blood type is obtained, and the patient is examined for shock. If shock is obviously present, as manifested by hypotension air hunger clouded sensorium or rapid thready pulse emergency blood transfusion is indicated Plasma may be used until whole blood is obtained Saline solution is a less satisfactory substitute Constant and careful clinical and laboratory observation is essential in these emergency patients in order to restore blood volume adequately and also to detect immediately evidence of further hemorrhage Facilities for emergency operation must be available should this become necessary

from superficial ulcers or erosions Meulengracht however has compared his statistics with those of Christiansen working under a similar hospital set up in Denmark in 289 patients treated with the old starvation gruel program Christiansen found a mortality rate of 7 9 per cent In 1943 Rasberry and Miller reported on 2111 collected cases of prompt feeding giving a gross mortality rate of 4 per cent excluding those moribund on admission or dying from other causes the net mortality was 1 9 per cent It is of course not entirely fair to exclude from such statistics patients who are too ill to eat when such cases are included in the statistics of other forms of therapy

In any case much credit is due Meulengracht for popularizing the principle of prompt feeding an approach which had been appreciated previously by Lenhartz and Andresen Many authorities question the wisdom of the routine use of the bulky meals of the Meulengracht diet particularly in seriously ill patients and many alternative diets have been suggested as being more easily consumed by the patient while still fulfilling the principles of prompt feeding

Medical versus Surgical Therapy The lowest recorded mortality for routine surgical therapy of chronic peptic ulcer during severe hemorrhage is that of Finsterer[10] who reported a mortality rate of 5 1 per cent in seventy eight cases operated upon within forty eight hours of the onset of hemorrhage Miller and Elsom[3] found an average mortality rate of 28 per cent in 383 collected cases treated surgically One must keep in mind of course that surgical therapy of bleeding ulcer is usually reserved for the more severe hemorrhages It is not reasonable to compare surgical mortality statistics with medical mortality without making certain comments Much of the mortality associated with surgical therapy is the result of excessive delay in operating upon a patient with continuous or recurrent hemorrhage yielding a patient who is in poor condition and a poor operative risk This is well shown in Table 37

Table 37 Difference in Mortality between Early and Late Operation for Bleeding Peptic Ulcer

(From the collected statistics of Ivy Grossman and Bachrach[17])

	TOTAL CASES	PER CENT DIED
Early operation (within 48–72 hours)	155	1 8%
Late operation (after 48–72 hours)	116	39 7%

The recent surgical literature has emphasized the increasing role of early operation in patients with severe hemorrhage (loss of half of the circulating red blood cells) a group which carries a high mortality on conservative therapy For example Stewart *et al*[30] report a mortality of 15 per cent for early operation (thirty three cases) as compared with a mortality of 29 per cent for an identical therapeutic regimen including massive transfusions but without operation (twenty one cases) Welch[31] stresses the need for operation in severely hemorrhagic patients who have recurrent bleeding while under observation or who have evidence of continuing hemorrhage after the administration of 2500 cc of blood (these latter patients will usually be over the age of fifty) His statistics show an operative mortality of 9 4 per cent for emergency operation within forty eight hours after onset of hemorrhage or after early recurrence of bleeding (thirty two

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In the less critically ill patient a more routine approach is possible A brief history is obtained particularly eliciting the presence of previous ulcer symptoms and determining whether previous roentgenograms demonstrated an ulcer deformity The extent of the hemorrhage can sometimes be judged by the estimated amount of hematemesis or the severity of the melena A gentle physical examination is performed taking care not to disturb the abdomen unduly Arrangements should be made for recording of the blood pressure and pulse every hour A complete blood count is done on admis sion and arrangements are made for repeat hemoglobin red blood cell count and hematocrit determinations at three hour intervals or more often in severe cases A daily blood urea nitrogen determination is desirable and in severe cases the urine output should be recorded

The history the clinical appearance of the patient and the laboratory studies listed should enable one to classify a hemorrhage as mild to mod erate or severe This is an important decision since severe hemorrhages may indicate potential surgical candidates In a continuing hemorrhage one should try to estimate the rate of bleeding Gross examination of saved vomitus and stool specimens will be of some help here following the blood count and hematocrit is also of help although they admittedly lag behind the clinical findings In a patient receiving transfusions who shows a de crease in blood count values the hemorrhage is obviously proceeding at a rate greater than he is being transfused If the rate of continuing hemor rhage is rapid an early decision for operation may be necessary If a patient does not clearly have hemorrhage from obvious peptic ulcer more complete initial investigation is indicated to rule out other causes of bleeding such as gastric carcinoma, liver cirrhosis gastritis or splenic anemia With regard to bleeding from esophageal varices due to cirrhosis if the physical findings do not obviously suggest cirrhosis a bromsulfalein retention test will usu ally settle the problem Other aspects of the differential diagnosis of gas troduodenal hemorrhage are discussed elsewhere (see Chap 59)

Dietary Management A prompt feeding program of some form is usually recommended in order to provide needed nutrition to serve as a buffer for

*Table 38 Bland Diet**

BEVERAGE	Milk Milk beverage	Coffee substitute
BREAD	Bread day old or toast white or rye) Butter crackers	Soda crackers Zwieback
CEREAL	Cornmeal Farina Hominy grits Oatmeal Prepared corn cereal	Prepared rice cereal Rice Fine whole wheat cereal Other whole wheat cereal strained
DESSERT	Bread pudding Cake (plain) Cookies (plain) Cornstarch pudding Custard Fruit puree whip	Gelatin dessert Ice cream or ice (plain or with fruit puree) Junket Rice pudding Tapioca pudding
FAT	Butter or vegetable shortening	
FRUIT	Any fruit puree or juice Fresh banana Canned and Royal Anne and Bing cherries	Peeled and cooked Apple Plums Apricots Prunes Peaches Rhubarb Pears

Table 38—Continued

MEAT OR SUBSTITUTE	Beef lamb pork veal roast broiled boiled, baked
	Cheese American, finely divided and in combination with other foods cottage cream
	Chicken stewed creamed broiled baked
	Eggs coddled poached soft cooked hard boiled creamed scrambled in a double boiler
	Fish fresh canned salmon or tuna boiled broiled baked creamed
	Liver boiled baked creamed
	Oysters or sweetbreads stewed creamed escalloped
POTATO OR ALTERNATE	Prepared in any way except fried macaroni noodles rice spaghetti Irish or sweet potatoes
SEASONING	Salt
SOUP	Cream soup made from allowed vegetables
SWEETS	Sugar syrup jelly and chocolate
VEGETABLES	Puree string beans beets corn peas spinach tomato
	Cooked tender asparagus tips carrots eggplant pumpkin squash
AVOID	1 Highly seasoned food and sauces catsup horseradish mustard pickles and condiments
	2 *Cabbage onions peppers radishes and turnips*
	3 Rare meat meat soup broth and gravy
	4 *Corned beef frankfurters sausage smoked meat and fish* or any prepared meats
	5 *Fried food hot bread and pastry*
	6 Nuts
	7 Very hot and very cold food unless eaten slowly
	8 Overeating

SAMPLE MENU

Breakfast	Noon	Evening
Orange juice	Creamed chicken	Strained cream of tomato soup
Cream of wheat	*Mashed potatoes*	*Scrambled eggs*
Toast	Green bean puree	Baked potato
Butter	*Bread*	*Pea puree*
Beverage	Butter	Bread
Cream	*Lemon cream pudding* with meringue	*Butter*
Sugar if desired	Milk	Applesauce
		Milk

Midmorning Midafternoon and Evening

Milk or milk beverage

Crackers cookie bread or cereal

EDITOR'S NOTE While prompt and frequent feeding rather than the composition of the *diet undoubtedly is of greater importance in treatment after hemorrhage some features of* this regimen warrant consideration Many authorities prefer the meats to be scraped *ground minced* or diced Some would object to the *inclusion of pork canned salmon* and tuna and oysters especially in treatment after massive hemorrhage Weak tea cocoa and *eggnog* (nonalcoholic) are satisfactory coffee substitutes

Most authorities however decidedly prefer *hourly feedings* of milk and cream or milk *and protein* powder mixtures as the ideal diet for most rapid healing of gastroduodenal ulcer In the ulcer complicated by bleeding all the criteria of ideal management are best *met* by an hourly feeding regimen In otherwise uncomplicated cases the addition of meat to this regimen on or after the fourth day in the form of broiled scraped beef balls tender *ground* beef lamb or veal seems desirable Ordinarily the patient is allowed to be up some time during the third week and therefore may begin the so-called three-meal management *program* However the hourly or two hourly milk and cream feedings between meals and after the evening meal are continued Such dietary program is carried out for a period of *six* months or longer

The modified Sippy diet is used extensively and in addition to the advantages mentioned by the authors of this chapter it is more suited to the treatment of hemorrhage For additional discussion of this diet the reader is referred to Chapter 30

gastric acidity and to keep enough food in the stomach to avoid hunger contractions The majority of patients treated today are given a soft, bland diet such as the modified Meulengracht diet outlined in Table 38 or the modified Sippy diet (Table 39) The authors prefer the bland diet outlined in Table 38 because of its greater nutritive value It is usually given in six feedings at 8 and 10 A M 12 noon 3 6 and 10 P M When more frequent

Table 39 Modified Sippy Diet

The usual schedule consists in the administration of 3 ounces of whole milk and 18 per cent cream (1½ ounces of each) *hourly from 7 A M to 7 or 9 P M for twenty one days*

If desired the milk cream mixture may be modified in various ways such as by using whole milk alone skimmed milk or powdered milk or by varying the quantity

When additional feedings are permitted they are substituted for one of the hourly milk and cream feedings at the time designated as follows

Day 1	Milk and cream only 7 A M to 7 or 9 P M
Day 2	10 A M Feeding 1
Day 3	10 A M Feeding 1
	4 P M Feeding 2†
Day 4	10 A M Feeding 1 or 3
	4 P M Feeding 2
	6 P M Feeding 3‡
Day 5	8 and 10 A M Feeding 4§
	4 and 6 P M Feeding 4
Day 6	8 and 10 A M 2 P M Feeding 4
	4 and 6 P M Feeding 4
Day 7–21	8 and 10 A M 12 noon Feeding 4
	2 4 and 6 P M Feeding 4

Egg soft cooked poached or scrambled in a double boiler

† Cereal Cream of Wheat Farina rice or any strained cereal

‡ Dessert custard tapioca junket cornstarch rice bread pudding and Jello—no chocolate

§ Foods for the day are to be selected from the following

- At least 2 eggs every day after day 4
- Cereal
- Strained cream of vegetable soup
- Avoid highly flavored vegetables and broths
- Vegetable juice or puree beet carrot celery corn lima bean pea pumpkin spinach squash string bean canned asparagus
- Dessert
- Milk toast

After the seventh day the following may be included in Feeding 4

- Cottage or cream cheese
- Prepared corn or rice cereal

Butter jelly sugar and salt may be used in moderation

Cream may be flavored with vanilla sugar

One of the following may be added to any feeding

- 1 slice of white toast or day old white bread
- 2 white crackers or plain cookies such as Scotties arrowroot vanilla wafers and sugar cookies

feeding is desired the diet can be adapted to any schedule—for example additional night feedings may be given in order to insure the presence of food in the stomach at all times or smaller more frequent feedings may be desired in a given patient in order to avoid possible overfilling of the stomach The diet is sufficiently selective so that servings of soft palatable food and liquids can be given the more ill patient in place of the more usual food

Some clinicians prefer the modified Sippy diet initially because of its

simplicity of routine and because of its avoidance of the danger of bulky meals a point of some importance in the very ill patient The chief objection to the Sippy type of diet is its nutritional inadequacy in its early stages The diet is virtually devoid of vitamin C is low in niacin iron and other minerals In use it should routinely be supplemented with ascorbic acid 75 mg daily (oral) Many alternative dietary regimens for use during hemorrhage are popular one of the simplest being hourly feedings of milk containing 10 per cent protein hydrolysate Another is the Andresen diet (Table 40) consisting initially of frequent feedings of a mixture of gelatin glucose cream and milk [2]

Table 40 Andresen Diet for Gastric Hemorrhage

GELATIN MILK MIXTURE	AMOUNT	CARBOHYDRATE	PROTEIN	FAT	CALORIES
Gelatin	30 gm		27 gm		100
Glucose	60 gm	60 gm			240
Cream (20%)	100 cc.	3 gm	3 gm	18 gm	180
Milk	900 cc.	36 gm	27 gm	27 gm	550
		99 gm.	57 gm	45 gm.	1000 (approx)

This formula is to be supplied by diet kitchen every 12 hours kept cool, but not in refrigerator to prevent jelling and served cool or warm

FEEDINGS AFTER GASTRIC HEMORRHAGE

For patients immediately after hematemesis
No feeding while patient is asleep
No ice water or other drinks to be given
Gelatin Milk mixture to be given cool or warm as follows

1st and 2nd days	4 oz. every 1½ hour
3rd, 4th and 5th days	5 oz every 2 hours
6th and 7th days	6 oz. every 2 hours

Now add to each of four feedings one of the following

1 soft boiled or poached egg
3 ounces of cereal
Custard Jello or ice cream

8th and 9th days As above only add 2 extras to each of 3 feedings
10th day and thereafter Ulcer diet.
Water beginning on 5th day increasing amounts starting with 1 oz. at a time.
Mineral oil, ½ oz. each night beginning on second night

If the patient is vomiting on admission to the hospital the diet must be withheld The blood chlorides carbon dioxide-combining power and blood nonprotein nitrogen should be checked This type of patient should be maintained on intravenous or subcutaneous fluids (at least 1000 cc of isotonic saline solution daily) until vomiting ceases Ordinary diet therapy can then be gradually resumed

Drugs Morphine should not be routinely used in these patients It has been shown that morphine relaxes the duodenal cap which may interfere with constriction of a vessel. Probably a more important contraindication is that morphine often interferes with the patient s eating by producing excessive sedation or even causing nausea and vomiting A mild sedative effect is usually desirable to allay the apprehension of the patient and anxious relatives This can be obtained with oral phenobarbital ½ grain (32 mg) every six hours When oral administration is not feasible because

gastric acidity and to keep enough food in the stomach to avoid hunger contractions The majority of patients treated today are given a soft bland diet such as the modified Meulengracht diet outlined in Table 38 or the modified Sippy diet (Table 39) The authors prefer the bland diet outlined in Table 38 because of its greater nutritive value It is usually given in six feedings at 8 and 10 A M 12 noon 3 6 and 10 P M When more frequent

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sary These can be given in the form of isotonic saline solution at least 1000 to 2000 cc daily by subcutaneous drip or slow intravenous drip A urinary output below 1000 cc a day is an indication for additional fluids

Special Procedures Slow intragastric drip of an alkalinized milk solution or a milk amphogel mixture has been recommended by some Not all patients tolerate well the discomfort of the tube necessary to this procedure and there does not seem to be any good reason for giving by tube solutions which could just as easily be taken by mouth Sometimes intragastric drip is alternated with intervals of gastric aspiration examination of the aspirate for blood may give early evidence of recurrent bleeding particularly from gastric ulcers However the presence of a tube in the stomach of a patient whose bleeding is of gastric origin may be of some danger in promoting further hemorrhage due to trauma

Kennedy Reynolds and Cantor[19] have used Gelfoam and thrombin in the control of gastroduodenal hemorrhage after demonstrating that these substances produced a "firm flat tenacious clot" which rapidly stopped experimental gastric hemorrhages in dogs In bleeding ulcer patients 2 tablespoons of Gelfoam powder (Upjohn) are mixed with 2 ounces of milk and cream and given to the patient orally every two hours Immediately after each dose the patients are given 250 units of thrombin orally in 50 cc. of water Aluminum hydroxide gel is given at regular intervals to prevent digestion of the clot, and the patients are otherwise on a full medical regimen for hemorrhage In twenty seven patients with massive gastroduodenal hemorrhage so treated there were no deaths In the past the use of hemostatic substances has been of little value in controlling ulcer hemorrhage but this procedure seems worthy of further trial as an adjunct to routine medical therapy

SURGICAL INTERVENTION DURING HEMORRHAGE

Operation when indicated is a life-saving procedure However every patient deserves an initial trial of conservative management regardless of the severity of the hemorrhage When this is obviously not succeeding in achieving cessation of hemorrhage operation must be considered Mild to moderate hemorrhage is not usually a surgical problem Heuer[15] estimates that 15 per cent of patients with *severe* hemorrhage will die if not operated upon. An appreciation of the prognostic factors mentioned previously will help one to spot patients who may require surgical intervention—particularly those over age forty five with sclerotic vessels patients with recurrent massive hemorrhage while receiving conservative medical therapy the patient with hematemesis the patient with severe anemia such as a hemoglobin of 8 gm (50 per cent) and of course the patient with continuous hemorrhage as shown by failure of the hemoglobin to stabilize in the face of transfusions Sufficient transfusion therapy must be used to avoid severe anemia or recurring shock, which will make such patients poor surgical risks Adequate blood replacement in potential surgical candidates will often permit a longer trial of medical therapy and give the physician more time to weigh the decision for operation But too much time should not be wasted in arriving at this decision because the mortality rate for operation rises sharply after forty-eight hours of hemorrhage

Persistent bleeding is evidenced by obvious recurrent hematemesis or

of nausea the same dose of sodium phenobarbital can be given hypodermically At all times oversedation must be avoided in these patients, whose cerebrum and respiratory center have already been subjected to considerable depression as the result of shock and anemia

Although there are objections in some quarters to the use of antacid therapy in ulcer hemorrhage *a bleeding ulcer is an active ulcer* and some form of antacid therapy seems indicated to promote ulcer healing particularly if pain persists after hemorrhage For this purpose 8 cc of aluminum hydroxide gel six times daily or magnesium trisilicate 1 or 2 gm six times daily are recommended Magnesium trisilicate tends to be less constipating than aluminum hydroxide gel Combined administration of these two drugs has been popularized in order to avoid the constipating effect of aluminum hydroxide gel used alone alternating doses of the two antacids may achieve this balance Individual preferences will frequently involve the use of other of the many available antacids as substitutes for these the relative merits of these other drugs are discussed elsewhere (see Chapters 29 and 30) Intestinal obstruction as a result of impacted blood and nonabsorbable antacids has been described but the danger of this is slight The absorbable alkalis such as sodium bicarbonate or related drugs are usually avoided because of their tendency to promote alkalosis and rebound gastric acid hypersecretion

Tincture of belladonna three times daily orally in sufficient dosage to cause dryness of the mouth or atropine sulfate 1/150 to 1/100 grain three times a day (oral or hypodermic) should be given for their effect on gastric motility and secretion Iron therapy is frequently irritating to the stomach and is best deferred until the hemorrhage has ceased

Transfusions Blood transfusions should be given in patients with severe hemorrhage Use of transfusions is usually necessary in patients with (1) shock as manifested by a systolic blood pressure below 90 or 100 mm of mercury and a pulse rate of 110 or more or clinical evidence of shock (such as syncope on sitting up air hunger or confused sensorium) (2) anemia with a hemoglobin of 8 gm (50 per cent) or a red blood cell count of 2 to 3 million (3) evidence of continuing or recurrent brisk hemorrhage particularly in a patient over age forty five who is likely to have sclerotic vessels (4) and in general in any patient who is a potential surgical candidate The amount and rate of blood given must be adjusted to the requirements of the individual patient Preferably transfusions should be continued until all manifestations of shock are alleviated and the hemoglobin concentration is restored

Delayed transfusions can of course be given in any amount a week or so after hemorrhage has ceased in order to speed convalescence

The importance of correcting dehydration is emphasized by Ivy *et al* Since considerable amounts of water and sodium chloride are lost from the body in massive hemorrhage a deficit in these items is likely to occur unless complete replacement of lost blood is made by whole blood transfusions The studies of Stewart and associates indicate that this is usually not the case [9] Ivy *et al* feel that the patient should have 2000 to 3500 cc of water and 10 to 15 gm of sodium chloride intake daily In the patient who is on a prompt feeding program this requirement is usually readily met by his oral dietary and fluid intake In the patient who is nauseated or vomiting or who is obviously dehydrated parenteral fluids become neces

sary These can be given in the form of isotonic saline solution at least 1000 to 2000 cc daily by subcutaneous drip or slow intravenous drip A urinary output below 1000 cc a day is an indication for additional fluids

Special Procedures Slow intragastric drip of an alkalinized milk solution or a milk amphogel mixture has been recommended by some Not all patients tolerate well the discomfort of the tube necessary to this procedure and there does not seem to be any good reason for giving by tube solutions which could just as easily be taken by mouth Sometimes intragastric drip is alternated with intervals of gastric aspiration examination of the aspirate for blood may give early evidence of recurrent bleeding particularly from gastric ulcers However the presence of a tube in the stomach of a patient whose bleeding is of gastric origin may be of some danger in promoting further hemorrhage due to trauma

Kennedy Reynolds and Cantor[19] have used Gelfoam and thrombin in the control of gastroduodenal hemorrhage after demonstrating that these substances produced a "firm flat tenacious clot" which rapidly stopped experimental gastric hemorrhages in dogs In bleeding ulcer patients 2 tablespoons of Gelfoam powder (Upjohn) are mixed with 2 ounces of milk and cream and given to the patient orally every two hours Immediately after each dose the patients are given 250 units of thrombin orally in 50 cc of water Aluminum hydroxide gel is given at regular intervals to prevent digestion of the clot and the patients are otherwise on a full medical regimen for hemorrhage In twenty seven patients with massive gastroduodenal hemorrhage so treated there were no deaths In the past the use of hemostatic substances has been of little value in controlling ulcer hemorrhage but this procedure seems worthy of further trial as an adjunct to routine medical therapy

SURGICAL INTERVENTION DURING HEMORRHAGE

Operation when indicated is a life-saving procedure However every patient deserves an initial trial of conservative management regardless of the severity of the hemorrhage When this is obviously not succeeding in achieving cessation of hemorrhage operation must be considered Mild to moderate hemorrhage is not usually a surgical problem Heuer[15] estimates that 15 per cent of patients with *severe* hemorrhage will die if not operated upon An appreciation of the prognostic factors mentioned previously will help one to spot patients who may require surgical intervention—particularly those over age forty five with sclerotic vessels patients with recurrent massive hemorrhage while receiving conservative medical therapy the patient with hematemesis the patient with severe anemia such as a hemoglobin of 8 gm (50 per cent) and of course the patient with continuous hemorrhage as shown by failure of the hemoglobin to stabilize in the face of transfusions Sufficient transfusion therapy must be used to avoid severe anemia or recurring shock which will make such patients poor surgical risks Adequate blood replacement in potential surgical candidates will often permit a longer trial of medical therapy and give the physician more time to weigh the decision for operation But too much time should not be wasted in arriving at this decision because the mortality rate for operation rises sharply after forty eight hours of hemorrhage

Persistent bleeding is evidenced by obvious recurrent hematemesis or

copious melena by a continuation of rapid pulse rate and a failure of the blood pressure to stabilize or other evidence of shock A sudden diuresis or syncope on sitting up may be the first indication that hemorrhage has recurred If it is not possible to maintain a safe blood volume with transfusions in the face of persistent bleeding operation is indicated

Test of Transfusion Observation of the clinical status and the blood hemoglobin level of the patient in the face of transfusion therapy will often aid in detecting patients with recurrent hemorrhage or patients with continuing hemorrhage who have a rate of blood loss too great to warrant further delay of operation This situation is readily apparent when it becomes impossible to restore the hemoglobin toward normal even after the administration of 2 liters of blood or if the administration of blood has restored the hemoglobin a further drop occurs within the following six to twelve hours If the hemorrhage has stopped 500 cc of transfused blood can be expected to raise the hematocrit by 5 per cent

The surgical candidate should have a known history of peptic ulcer or previous x ray evidence of peptic ulcer Scott [8] found that in hematemesis patients reporting pain of more than one month s duration three of four will have chronic peptic ulcer in those with pain of less than one month s duration one of four will have chronic peptic ulcer If operation is seriously considered in the face of indefinite clinical evidence of peptic ulcer a roentgenogram should be done even during active bleeding If the roentgenologist is warned to use extra care during his examination the procedure can be done without much danger to the patient

Hampton[13] described a technic for x ray examination of these patients during bleeding The examination is done with the patient in the face up horizontal position a heavy barium suspension is used and the normal gas bubble in the stomach is used for double contrast palpation or compression of the abdomen is not entirely necessary Welch[31] states that a positive diagnosis of ulcer was made within forty eight hours after admission to the hospital in 85 per cent of the cases in which this technic was used

Operation may be justified even in patients in whom a definite diagnosis of peptic ulcer has not been made Indeed in such patients no lesion may be apparent at the time of operation at least by external examination of the stomach duodenum and upper intestine In such a case the surgeon should perform a gastrotomy or duodenotomy in order to detect the presence of a bleeding point which may not be apparent by external examination or palpation Should no lesion still be found the problem confronts the surgeon as to whether the operation should be terminated or whether a partial gastrectomy should be carried out Some of the evidence is in favor of the performance of a gastrectomy if the patient s condition permits it [30] The rationale for such a procedure is the presence of gastritis in the antrum and middle of the stomach acute single or multiple ulcerations which may be the source of the hemorrhage but particularly that such a procedure by lowering the acidity may reduce the likelihood of superficial erosions as a cause of the hemorrhage Indeed Crohn Marshak and Galinsky[9] suggest that subtotal gastrectomy with bilateral vagotomy may be the final answer to repeated gastroduodenal hemorrhage of unexplained origin

There is by no means unanimity of opinion as to the proper surgical handling of gastroduodenal hemorrhage of uncertain origin At the present time the authors doubt the wisdom of routine gastrectomy in cases in which

gastrotomy and duodenotomy are negative having observed several patients with recurrent hemorrhage despite operation Undoubtedly the procedure is warranted in selected cases depending on the individual circumstances A final decision on this issue must await the presentation of thorough statistical studies on the results of the procedures mentioned

Severe pyloric obstruction associated with massive hemorrhage is usually an indication for surgery Acute perforation with hemorrhage requires emergency operation

The operation of choice in bleeding peptic ulcer is subtotal gastrectomy with removal of the ulcer Removal of a duodenal ulcer which is penetrating the pancreas may be too difficult or time consuming in a critically ill hemorrhagic patient This sometimes necessitates doing a lesser procedure such as resection with exclusion of the duodenum and ulcer If the ulcer is *bleeding at the time of the operation* it is usually advisable to ligate the gastroduodenal artery and its branches the right gastro-epiploic and the superior pancreaticoduodenal vessels

All indications and arguments for surgical therapy of bleeding ulcer are based on the assumption that a competent surgeon is available It has been suggested that a surgeon whose operative mortality in elective gastric surgery exceeds 5 per cent should not be selected to operate on patients with bleeding peptic ulcer[11] If a skilled surgeon is not available continued medical management is indicated

ELECTIVE SURGERY AFTER RECOVERY FROM HEMORRHAGE

The risk of subsequent hemorrhage in a patient who has recovered from a first gastroduodenal hemorrhage is uncertain undoubtedly it will be influenced by the adequacy of the medical program which he follows Haraldson[14] followed up 205 patients on a conservative program for ten years after hemorrhage fifty four had recurrent hemorrhage (three fatal) In a follow up of five years or more of 134 patients after hemorrhage Holman[16] found that 50 per cent bled again and 3 7 per cent died from hemorrhage On the basis of these reports the incidence of subsequent hemorrhage appears to vary from 26 to 50 per cent, and the incidence of death from subsequent hemorrhage varies from 1 4 to 3 7 per cent Thus although the possibility of a second hemorrhage is high the risk of death is less than during a first hemorrhage

Interval surgery should be considered in a patient who has had three or more hemorrhages and who is over fifty years of age or is younger with premature arteriosclerosis (such patients "look older") Otherwise continued medical management of the ulcer is indicated after hemorrhage unless some other ulcer complication is present requiring surgical attention

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Chapter 61

GASTRIC RETENTION

S ALLEN WILKINSON AND ELMER W HEFFERNON

Gastric retention is a matter of serious concern to the medical man and to the surgeon alike In the past gastric retention has been accepted as one of the unpleasant complications of peptic ulcer and also of malignant dis ease of the stomach It has other causes which will be discussed later A brief review of the literature indicates a surprising paucity of articles con cerning this complication in the last ten or fifteen years and most writers indicate that the problem of gastric retention requires many weeks of hos pital time before a decision can be reached regarding the need for opera tion or the desirability of medical management

Rafsky[8] presented a method of medical management of gastric retention by duodenal alimentation Collins and Rossmiller[3] described the importance of medical management in patients with obstructive symptoms who might not have real pyloric obstruction LaPorte[4] outlined a plan of treatment of a pyloric obstruction with diathermy Boles [1] writing on the medical man agement of complications of peptic ulcer advised lavage of the stomach morning and night Thompson[1] advised daily aspiration over a period of several weeks in order to determine the eventual course of an obstructing lesion Paul[7] suggested that some cases of gastric retention were more apparent than real and advised aspiration of the stomach three hours after the last meal of the day Other writers [6 9 10 11] present methods of manage ment varying from no feedings by mouth to hourly feedings by mouth with aspirations varying from continuous suction to once daily all having the common denominator of requiring from ten days to six weeks in order to prepare the patient for operation

DIAGNOSIS OF GASTRIC RETENTION

Because gastric retention may be due to functional disease it is important to be aware of the various causes for functional gastric retention and to decide upon the treatment of this condition early in the course of the dis ease It is not uncommon to see people who have been subjected to gastro enterostomies or other procedures to relieve an obstruction which was not actually present. In any acute infection particularly in the prodromal stage pylorospasm and gastric retention are the rule The problem of the ill child who starts with vomiting the food he had eaten the night before only to have an acute exanthematous disease develop within the next twelve hours is a well known one A pneumonic process either in a child or an adult may be ushered in by pylorospasm and vomiting Organic dis ease higher in the stomach particularly an acute and active gastric ulcer high on the lesser curvature will frequently produce enough spasm of the pylorus so that vomiting is the most common complication and it may so overbalance the pain in a particular case that the patient may minimize the pain Not only will vomiting occur in these cases but actual gastric dilatation may occur and persist for several days giving the appearance

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until the point of actual gastric retention is reached Gastric hemorrhage and anemia are not early symptoms of malignant lesions of the stomach When these have occurred in combination with obstruction the lesion is usually far advanced and while it may be removable locally metastatic lesions occur promptly and almost inevitably

The diagnosis of retention can be made in most instances from a careful history The diagnosis should be confirmed in all instances with adequate fluoroscopic study of the stomach and x ray films taken not only at the time of the fluoroscopic examination but at sufficient intervals thereafter to demonstrate real retention Occasionally a large and apparently dilated stomach is seen fluoroscopically but it may be noted to empty in approximately normal time showing that the obstruction which may be present is negligible or slight Physical examination will frequently reveal a succussion splash and the outline of the stomach can usually be percussed indicating its approximate size and enabling the observer to follow the progress of treatment in reducing its size

Gastric aspiration will quickly reveal an abnormal amount of fluid in the stomach particularly since the aspiration is usually done on a fasting stomach If a large dilated stomach is found fluoroscopically it is wiser after the fluoroscopy to aspirate the stomach at once rather than to permit the barium to remain too long in the stomach to determine the full extent of the obstruction Enough barium will remain in the stomach despite the aspiration so that an adequate determination can be made of the emptying time

It has been suggested that the fluoroscopic observation of gastric obstruction is not completely accurate since the stomach is in a fasting state and barium is so much heavier than food that more obstruction appears than is actually present A method of giving a small amount of food mixed with a small amount of barium with the stomach in a fasting state may be more physiologic

MANAGEMENT OF GASTRIC RETENTION

There are a number of methods by which gastric retention can be managed and in the hands of competent observers most of them work well At the Lahey Clinic we have devised a method which is to be reviewed here[14, 15]

The conventional plan of management is adequate for the control of slight degrees of retention Bed rest antispasmodics and nonabsorbable alkalies are the primary measures To control the tendency to retention the stomach should be emptied by tube twice daily The more important aspiration is at bedtime As the patient improves this bedtime aspiration will decrease to 3 or 4 ounces (90 to 120 cc) If as a result of vomiting there is evidence of dehydration if the electrolytes chlorides sodium carbon dioxide or potassium levels are abnormal the feedings by mouth must be supplemented with isotonic saline solution dextrose in saline solution or protein hydrolysates intravenously In the mild cases the usual milk and cream feedings can be given at frequent intervals throughout the day as one would normally treat an ordinary ulcer For details concerning the management of cases of alkalosis the result of chloride loss and at times of excessive absorbable alkali intake see Chapter 62

A more rapid method for the control of retention is the familiar Wan

of an organic obstruction at the pylorus when none really is present These conditions can all be listed under the heading of reflex pylorospasm

In the organic group ulcer at or near the pylorus is the commonest cause *of gastric retention The retention in this case* may be due to the active disease process and may be the result largely of edema This particular type of retention is peculiarly susceptible to a few days careful medical regimen to be described later *On the other hand the retention may be the result* of cicatricial contraction and scarring This is usually the case when the ulcer is postpyloric and particularly so when it is in the first portion of the duodenum immediately beyond the duodenal cap Peptic ulcer because of its known tendency to periodicity shows a similar tendency to periodic obstruction with relief of the obstruction simply due to the normal remissions that seem to be a part of the disease process For that reason obstruction may subside spontaneously at the time we elect to treat it and we may erroneously give ourselves credit for the relief of the condition On the other hand a persistent and unrelieved obstruction of severe degree definitely increases the tendency to perforation in a badly eroded ulcer and perforation secondary to such obstruction is by no means an uncommon complication In these circumstances rupture of the stomach is exceedingly rare *but an occasional rupture of the esophagus due to persistent vomiting has* been reported[5] and has occurred in our series of cases

Obstruction due to ulcer can manifest itself insidiously with a gradual increase in vomiting occurring over a number of weeks More often however it begins suddenly after a period of increasing ulcer distress The principal symptom is vomiting one or more times daily Pain is often present and is temporarily relieved by vomiting The vomited material increases in amount and in its fluid content as the obstruction progresses

In subsensitive patients vomiting without pain and without any other ulcer symptoms may be the only complaint These people often have greatly dilated stomachs and present themselves with marked weight loss as a result of the duration of the process before they seek help

The differential diagnosis is usually easy The characteristic ulcer history *the findings of a high acidity and the absence of an intragastric filling* defect help to rule out malignancy In the case of intragastric polyps there are two differentiating points achlorhydria is the rule and the roentgenogram will demonstrate a filling defect which is obviously not an ulcer Hypertrophy of the pyloric muscular ring is most often found in those who *have had a lifelong history of vomiting Ulcer symptoms will be lacking* If the retention due to this cause is severe decompression of the stomach and eventual operation will be necessary just as in an obstructing ulcer

Gastric retention due to tumor is not as common as retention due to benign ulcer but it is common enough so that tumor cannot be ruled out *without careful and adequate study The tumor may be* a benign lesion such as a polyp If the polyp has a long pedicle the obstruction may be intermittent whereas if the tumor is an intramural one in the region of the pylorus the obstruction will be gradual and increasing A malignant tumor usually carcinoma of the stomach produces a steadily increasing obstruction A tumor located close to the pylorus may fortunately produce an early obstruction whereas if it is somewhat more distant from the pylorus it will have to grow *to a large size before producing actual ob*struction and as is well known there may be no symptoms of any kind

Among the advantages of this type of control of gastric retention are the ease with which it is administered in a hospital and the freedom from a complicated or mechanized hook up the readiness with which the patient *may be fed and some degree of nutrition maintained the decompression* of a large dilated stomach so that at operation the stomach will be found reduced to normal or nearly normal size This has a decided advantage from the surgeon s viewpoint He is not faced with the necessity of putting stitches in a stomach wall which is paper thin and he can better judge the size of his stoma In addition this method quickly allows the differentiation between a functional and an organic obstruction The functional obstructions will respond within forty eight hours and those organic obstructions

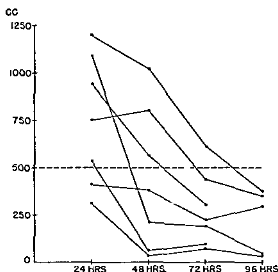


Fig 150 Gastric retention. Drainage return for each twenty four hour period of alternate feeding and suction Representative curves showing reduction in gastric retention within three days No operation was necessary

which do not respond within seventy two hours can safely be considered surgical and further valuable hospital time need not be allocated simply in determining whether the patient should or should not be operated upon Needless to say in dehydration the usual methods of supportive measures applicable to any case of severe dehydration should be used These should include adequate amounts of fluids intravenously or subcutaneously parenteral vitamins and such sedation as may be necessary to relieve the pain and apprehension of the patient at the beginning of treatment

It has been stated at times that the method of alternate feeding and suction presented here will not allow an adequate period of stomach rest and will result in a congested stomach at operation By the more conservative methods of management a period of two to four weeks is utilized to accomplish this without any guarantee of success The feeding and suction method by trial on a large group of patients has been found adequate in allowing time for hydration of the patient for balancing of his electrolytes for decompressing the stomach and for relieving congestion If the obstruction is severe and intractable enough to require operation no amount of

gensteen[13] method of suction whereby a constant suction is maintained on the stomach through a system of gentle negative pressure maintained by a hydrostatic arrangement of two water bottles This method is well known and it works satisfactorily when complete emptying of the stomach is de sirable and when such emptying should be maintained for any considerable period of time

Sandweiss[9] reported the use of Wangensteen suction attached to a Levin tube in the treatment of gastric retention He keeps his patients on con tinuous aspiration in this manner for three or four days They are allowed to have clear fluids orally ad lib and are allowed to be ambulatory with the tube disconnected from the suction apparatus for short periods of time Fluids and vitamins are given parenterally Several cases are cited of pa tients who did well on this program after treatment for only seventy two hours

Many hospitals today are equipped with suction machines which will maintain a graduated degree of constant suction These machines are small and the apparatus is simple The machine is electrically operated and if more suction is desired temporarily it is readily obtained by this method

The method used at the Lahey Clinic consists in introducing a rubber or plastic tube by way of the nose into the midportion of the stomach The contents of the stomach are aspirated on the introduction of the catheter and from that time on the patient is fed 3 ounces of a noncurding mixture such as malted milk made with water every hour on the hour throughout the twenty four hours This allows the introduction of 72 ounces of nutrient fluid a day In this may be put such alkalinizing agents as are deemed neces sary After introduction of this fluid mixture into the stomach the tube is clamped for thirty minutes of each hour At the end of thirty minutes the end of the tube is lowered into a bottle with the tip of the tube under water Thus a siphonage is constantly maintained the head of the column of water being the distance from the patient s stomach to the bottle beneath the bed The stomach is allowed to drain into the bottle for the succeeding thirty minutes of each hour At the end of the twenty four hours the total amount that has drained into the bottle is measured and any part of it that is desired may be collected for further examination If the gastric re tention is of a high grade the return for twenty four hours will exceed the total intake and may go as high as 90 ounces (approximately 3000 cc) a day If the obstruction is due to edema or spasm the amount which will return per day decreases rapidly and by the end of the second or third day usually will have dropped to less than 20 ounces or somewhat less than 500 cc Along with the relief of the obstruction there is an almost immediate relief of the pain which the patient complained of and he may be so much more comfortable that he may actually ask that the tube be left in place when in the judgment of the physician it is time to remove it

When the total amount of twenty four hour drainage is reduced to 500 cc a day or less the tube can safely be removed and the patient can be fed in the usual manner and the obstruction will not recur If however by the end of three days of this type of drainage the retention has not been reduced to less than 500 cc it can then safely be stated that the obstruction is organic in origin that further treatment will not be of value and that the patient should be operated on without further effort to reduce the retention

four hour return on drainage of more than 1000 cc Operation showed a congenital pyloric stenosis



Fig 152 Congenital pyloric stenosis in a 50 year old woman

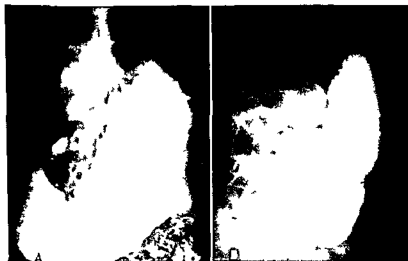


Fig 153 A Duodenal ulcer with gastric retention successfully treated by drainage B Same patient after one week s treatment

Case 2 A fifty three year old white man had a history of duodenal ulcer of many years He was admitted complaining of severe epigastric pain unrelieved by food and severe enough to prevent work His stomach was dilated and contained a large amount of fluid Peristalsis was obstructive in character On drainage the return from the drainage

further treatment will accomplish more than this In addition the saving to the patient in hospital days as well as the saving to the hospital (permitting more rapid turnover of these difficult patients) is a real economic factor

This method has been used at the Lahey Clinic on more than 400 patients with varying degrees and kinds of gastric retention It is equally

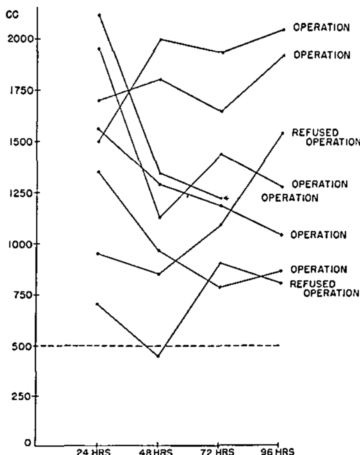


Fig 151 Gastric retention Drainage return for each twenty four hour period of alternate feeding and suction Representative curves showing failure to respond to drainage within three days Operation was advised or carried out in all cases

useful in the postoperative period when the patient has begun to take food by mouth but apparently has enough edema of the newly made stoma so that the food will not pass through Its use preoperatively allows the selection of the surgical patient and the elimination of the patient who might be a candidate for operation but who will respond to medical measures Figures 150 and 151 show the results in a group of surgical and nonsurgical cases

CASE HISTORIES

Case 1 A fifty year old white married woman had a six year history of intermittent vomiting associated with a steady weight loss of 17 pounds X ray studies showed a greatly dilated stomach containing fluid (Fig 152) The pyloric canal was narrow and elongated the duodenal cap appeared normal. After three days of drainage she still had a twenty

four hour return on drainage of more than 1000 cc. Operation showed a congenital pyloric stenosis



Fig 152 Congenital pyloric stenosis in a 50-year old woman

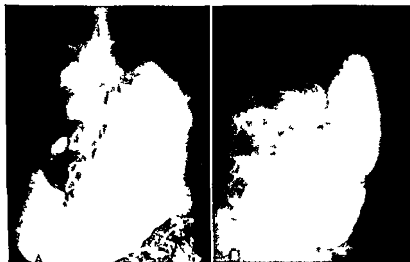


Fig 153 *A* Duodenal ulcer with gastric retention successfully treated by drainage *B* Same patient after one week's treatment

Case 2 A fifty three year old white man had a history of duodenal ulcer of many years He was admitted complaining of severe epigastric pain unrelieved by food and severe enough to prevent work His stomach was dilated and contained a large amount of fluid Peristalsis was obstructive in character On drainage the return from the drainage

tube decreased rapidly and by the end of the fourth day his drainage was down to 90 cc The tube was removed and on routine ulcer management with normal feedings he felt completely well and was discharged from the hospital in excellent condition A follow up one year later shows no further evidence of obstruction and he is feeling well

Case 3 A nineteen year old boy had a two year old history of duodenal ulcer with typical pain and remissions X ray studies showed a greatly dilated stomach and delayed emptying of the stomach The duodenal cap was irritable and grossly deformed After three days drainage he still had a return of approximately 1500 cc a day At operation a perforating ulcer producing scarring and marked stenosis of the duodenum was removed He has been well and normal in every respect for the succeeding six years

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Chapter 62

ELECTROLYTE DISTURBANCES IN PEPTIC ULCER

JOSEPH B KIRSNER

ETIOLOGIC AND CONTRIBUTING FACTORS

Alkalosis the most important disturbance in the acid base balance of the blood complicating peptic ulcer occurs as a result of an increase in serum bicarbonate and *p*H and of a decrease in the concentration of chloride (Table 41) It may result from the excessive intake of soluble alkali (so

dium bicarbonate) the depletion of chloride induced by loss of gastric juice or from a combination of these factors Inasmuch as sodium bicarbonate is no longer used routinely in therapy this type of alkalosis now is encountered only in persons chronically addicted to baking soda The principal cause of electrolyte imbalance in patients with peptic ulcer is the loss of chloride resulting from the vomiting or aspiration of acid gastric content. The prolonged use of a low salt diet such as characterizes the ulcer regimen may increase the tendency to hypochloremia Massive hemorrhage

Table 41 Representative Alterations in Serum Electrolytes Complicating Peptic Ulcer

	CARBON DIOXIDE (mM/L)	CHLORIDE (mM/L)	pH
Normal	27–30	95–105	7 35–7 45
Mild alkalosis	30–35	90–95	7 46–7 50
Moderate alkalosis	35–40	80–90	7 50–7 60
Severe alkalosis	40–60	60–80	7 60–7 65

will intensify an existing alkalosis because of the further loss of chloride and the decrease in renal function secondary to reduced blood volume anoxemia and hypoproteinemia. The tendency to an increased plasma bicarbonate in patients with pulmonary emphysema may be a contributory factor in such cases

OSMOTIC RELATIONSHIPS

Remarkably efficient physicochemical processes operate to maintain the osmotic equilibrium electroneutrality and the normal hydrogen ion concentration of body fluids The development of alkalosis signifies that these regulatory mechanisms have been overcome The biochemical disturbance is accompanied by shifts in water reciprocal changes in bicarbonate ion and by alterations in the renal excretion of water and electrolytes to preserve above all else normal osmotic concentrations in body fluids

The extracellular fluid (plasma and interstitial fluid) is composed chemically of basic and acid ions The principal basic ion is sodium the chief acid ions are chloride and bicarbonate Electroneutrality requires a constant balance of these ions as shown graphically and quantitatively in Figure 154 Thus a rise in sodium as in the alkalosis caused by soluble alkali is balanced by a proportional increase in bicarbonate The osmotic value of the extracellular fluid is determined by the sum of basic and acid ions and principally by the concentration of sodium Changes in the acid ions are less significant in this respect, since a decrease in chloride is offset by a reciprocal rise in bicarbonate thereby preserving the total concentration of acid ions Loss of sodium on the other hand is not replaceable except from the diet or the parenteral administration of salt. Deficit of this ion therefore diminishes the concentration of basic ions and automatically lowers the total ionic content a proportional quantity of water is lost to maintain osmotic equilibrium Conversely an increase in the concentration of sodium and in the total ionic content is accompanied by a rise in the volume of extracellular fluid

Ionic, osmotic and acid base equilibria also are maintained between the

extracellular and intracellular fluids Water passes freely between these compartments in the direction which will preserve normal osmotic concentrations In severe alkalosis the shift of water into the cells in response to the lowered osmotic pressure in the extracellular fluid may further decrease the water in this compartment In addition potassium an intracellular ion may pass into the extracellular fluid and sodium and chloride may migrate from the plasma into the cells According to Darrow and Pratt [6] the shift of sodium from extracellular to intracellular fluids, and vice

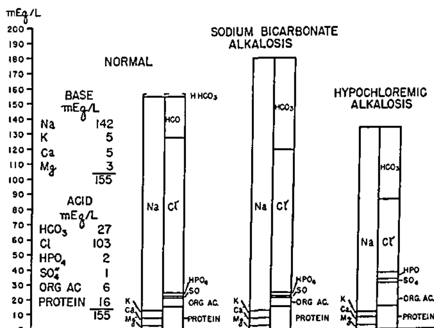


Fig 154 Diagrammatic representation of the normal electrolyte pattern of extracellular fluid and the changes characteristic of sodium bicarbonate alkalosis and hypochloremic alkalosis (Modified after Gamble)

$$\text{mEq/L} = \frac{\text{mg per liter}}{\text{atomic wt}} \times \text{valence}$$

versa is an important mechanism for diminishing the variations in extracellular bicarbonate The deficit of water in severe alkalosis ultimately may include significant losses of intracellular fluid Thus alterations in the electrolyte composition of the plasma particularly in the concentration of sodium always involve shifts in body water these changes take place not only in the plasma and within the cells but also and to a greater extent in the interstitial fluid If the loss of electrolyte is proportionately greater than that of water the electrolyte concentration in serum will diminish (so called "hypotonic" dehydration) In "hypertonic" dehydration the proportionately larger depletion of water leads to an increased concentration of electrolytes in serum The depletion of salt and water and the altered osmotic relationships are the most important chemical and physiologic consequences of alkalosis

Throughout this chapter mEq /L is the same as mM /L (or m M per liter) They have been used interchangeably by the author

ROLE OF THE KIDNEY

The kidneys play an indispensable role in maintaining the stability of the body fluids They preserve osmotic equilibrium by regulating the rate of water excretion in the urine thereby protecting against excessive hydra tion or dehydration they sustain the normal electrolyte pattern by con trolling the output of individual ions and they help maintain the normal *p*H of the blood by regulating the acidity of the urine and the rate of excre tion of electrolytes The response of the renal tubular epithelium to hor monal influences from the posterior pituitary gland and the adrenal cortex and proper functioning of the cardiovascular system are essential mech anisms in the control of osmotic concentrations of body fluids Impairment of kidney function due to preexisting renal disease or produced by dehy dration with renal vasoconstriction and diminished renal blood flow seri ously interferes with the regulation of acid base balance it is a most important factor in the development of alkalosis and in determining the severity of the biochemical disturbance

ALKALOSIS OF SODIUM BICARBONATE

The administration of soluble alkali (sodium bicarbonate) usually re sults in the absorption of increased quantities of sodium bicarbonate into the blood the excess base includes both alkali ingested and also to a lesser extent bicarbonate from the intestinal secretions made available for reabsorption as a result of the prior neutralization of hydrochloric acid in the gastric content. The acid base balance is not disturbed provided renal function is normal and sufficient water is available so that the base is eliminated as rapidly as it is absorbed The tolerance for sodium bicarbon ate may be remarkable as in the case of a young man with duodenal ulcer who received 32 000 gm of this alkali during a period of twenty months without significant change in the acid base balance and in the urea clear ance Persistent alkalosis develops when the excretion of the excess base is retarded because of decreased renal function The serum sodium total base bicarbonate and *p*H rise (Fig 154) The calcium phosphorus and chloride diminish slightly probably as a result of the accompanying in crease in plasma volume The output of sodium bicarbonate in the urine is elevated and the *p*H rises sometimes attaining a maximum of 7 8 The excretion of chloride decreases the output of ammonia likewise diminishes or ceases completely Nausea and vomiting accompanying the alkalosis will intensify the biochemical disturbance because of the loss of water and chloride the reduced volume of urine and the interference with renal regulation of the acid base balance

Alkalosis directly attributable to calcium carbonate does not occur owing to *the relative lack of absorption of this antacid Large single doses* of 10 or 15 gm infrequently may induce a minimal and transient rise in the serum calcium In the absence of chloride loss the serum electrolytes remain within normal limits during the prolonged daily ingestion of 20 to 30 gm of calcium carbonate The urinary excretion of calcium rises slightly whereas the outputs of phosphate ammonia and chloride diminish the *p*H of the urine rises but remains within the acid range The output of chloride in the feces is not increased significantly Similar changes in mineral excretion occur also during the ingestion of aluminum hydroxide

a completely nonabsorbable antacid The alkalosis occasionally observed *in patients receiving calcium carbonate during the "Sippy" treatment of* peptic ulcer almost invariably is attributable to the loss of chloride resulting from gastric aspiration vomiting and the inadequate intake of salt the acid base balance in such instances is restored to normal by the administration of sufficient quantities of sodium chloride and fluid even though the intake of calcium carbonate is continued (Fig 155)

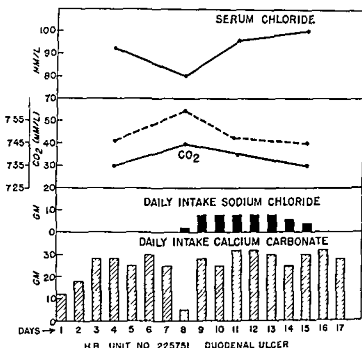


Fig 155 Hypochloremic alkalosis during Sippy treatment resulting from gastric aspiration acid base balance restored by increased intake of sodium chloride the intake of calcium carbonate being maintained

ALKALOSIS OF CHLORIDE LOSS

The normal stomach under fasting conditions secretes approximately 1000 cc of acid gastric juice daily containing a preponderance of hydro chloric acid and smaller quantities of the chlorides of sodium and potassium chiefly sodium In duodenal ulcer the twenty four hour volume of secretion is at least 2000 to 2500 cc and the output of chloride is two to three times larger than normal The water and electrolytes are derived from the blood and although the electrolyte pattern varies the gastric juice is practically isotonic with the blood In normal circumstances these ions are reabsorbed after the gastric content enters the small intestine the chloride reassociates with the sodium from which it was dissociated in the formation of hydro chloric acid and sodium bicarbonate passes from the plasma into the intestinal secretion thereby restoring the normal electrolyte pattern Failure of the chloride ion to return to the blood because of the vomiting or aspiration of gastric content results in hypochloremia and alkalosis

The severity of the chemical disturbance depends upon the quantity of

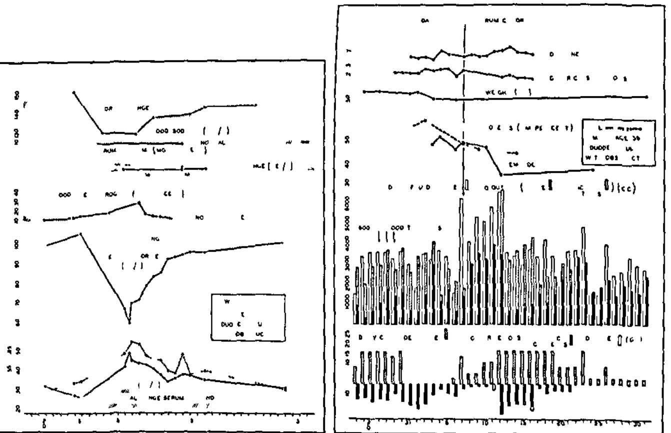


Fig. 150 Severe hypochloremia and alkalosis in a patient with duodenal ulcer induced by continued gastric aspiration. Alterations in serum electrolytes, associated biochemical abnormalities, fluid balance, chloride intake and output

electrolytes in the gastric juice The loss of large amounts of highly acid gastric content induces a severe depletion of tissue and plasma chloride and a smaller deficit of sodium the plasma bicarbonate increases in proportion to the chloride loss and associates with the sodium normally equivalent to chloride In the withdrawal of gastric content containing little or no hydrochloric acid depletion of chloride is less pronounced and the bicarbonate excess is correspondingly smaller indeed the acid base equilibrium may not be disturbed Thus hypochloremic alkalosis is more likely to develop in the patient with duodenal ulcer and gastric hypersecretion than in the normal person or the patient with gastric ulcer The quantitative differences in volume of secretion and gastric electrolytes between these groups are highly significant (Table 42) Curiously the stomach may continue to secrete large amounts of highly acid gastric juice despite extreme depletion of the serum electrolytes

Table 42 Sodium Potassium and Chloride in Twelve Hour Nocturnal Gastric Content of Normal Persons and Patients with Gastric Ulcer and Duodenal Ulcer

	CONCENTRATIONS				12 HOUR OUTPUTS		
	Na	*K* (m Eq /L)	*Cl*	*Volume* (cc)	*Na*	*K* (m Eq /L)	*Cl*
Normal (31 persons)	72	12 4	128 5	4,7	32	6 1	69 1
Gastric ulcer (21 patients)	82	14 4	126	583	43 9	8 5	78 4
Duodenal ulcer (64 patients)	58 1	12 6	141	1023	57 7	12 [illegible]	145 6

The hypochloremia and alkalosis may be extremely severe as in the following case

Unusually Severe Hypochloremia and Alkalosis Secondary to Vomiting

Case 1 S R a man aged thirty nine had a duodenal ulcer with high grade stenosis and frequent episodes of vomiting for ten years more pronounced during the two months preceding hospitalization The serum chloride was 72 2 mM per liter the carbon dioxide content 45 2 mM per liter and the *p*H 7 52 The alkalosis was corrected after several days of treatment with isotonic saline solution 5 per cent dextrose in isotonic saline solution and Ringer s solution Aspiration of the stomach later resulted in another episode of severe alkalosis despite the oral administration of 8 to 10 gm of sodium chloride daily The serum chloride measured 85 mM per liter the carbon dioxide content 42 mM per liter and the *p*H 7 54 The administration of dextrose in isotonic saline solution intravenously sodium chloride by mouth and the discontinuance of gastric aspiration again restored the acid base balance

The patient reentered the hospital one year later after ten days of intense vomiting He was lethargic and disoriented Physical examination disclosed a blood pressure of 96/58 and mild carpopedal spasm The serum calcium was 7 1 mg per cent (normal 9 to 11 mg per cent) The blood urea nitrogen was 99 8 mg per cent later decreasing to 47 mg per cent. The severity of the alkalosis was as shown in table on page 665

The characteristic chemical changes in this type of alkalosis are marked decrease in serum chloride reduction in sodium but relative excess of this ion now available for association with bicarbonate increase in bicarbonate and an elevated *p*H (Figs 154 and 156) The loss of sodium decreases the total ionic concentration and accordingly the volume of extracellular fluid Hemoconcentration occurs as indicated by an increase in the hematocrit The blood urea nitrogen rises because of the lack of sufficient water for the

Date	SERUM ELECTROLYTES			THERAPY
	Chloride	CO_2 (mM/L.)	pH	
8/18/4[illegible]	43 0	60 0+		1500 cc of isotonic saline 1500 cc 2% NH_4Cl in distilled water 1500 cc. 5% dextrose in isotonic saline 500 cc. 2% NH_4Cl
8/19/47	85 0	33 7	7 43	2000 cc 5% dextrose in isotonic saline continued vomiting
8/20/47	87 0	39	7 6	3000 cc. 5% dextrose [illegible] saline 400 cc 2% NH_4Cl
8/21/47	97 0	27 0	7 43	

excretion of nitrogenous waste products and the increased tissue catabolism accompanying dehydration The degree of nitrogen retention is related to the severity and rapidity with which electrolytes and water are lost the values occasionally approach uremic levels The azotemia subsides promptly after the restoration of electrolyte and fluid balance and the reestablishment of an adequate flow of urine A deficiency of potassium may occur in severe alkalosis

Several factors contribute to the hypokalemia, including (*a*) liberation of potassium through cellular breakdown and abnormally excessive excretion of this ion by the kidney (*b*) loss of potassium in the vomited or aspirated gastric content (Table 42) and (*c*) lack of intake of potassium It should be noted also that the administration of sodium chloride tends to increase the urinary excretion of potassium

The diminished volume of extracellular fluid leads to a reduction in the volume of urine The pH is alkaline because of a relative excess of base The output of chloride is markedly reduced or absent the production and excretion of ammonia likewise cease completely The deficit of sodium ultimately may be so great that none is available for excretion with bicarbonate and the reaction of the urine may become acid (pH 5 to 6) The urine not infrequently contains albumin casts and red blood cells Renal insufficiency may result in the retention of acid metabolites such as sulfates and phosphates partially decreasing the elevated plasma bicarbonate concomitant alterations in the excretion of water and electrolytes further intensify the acid base disturbance Starvation ketosis may develop with the appearance of ketone bodies (beta hydroxybutyrate and acetoacetate) in the urine

EFFECT OF ALKALOSIS ON THE KIDNEY

Kidney function frequently is impaired in alkalosis especially in the presence of antecedent renal disease and in patients with pronounced alterations in serum electrolytes An initially normal urea clearance may decrease by 50 per cent in preexisting renal disease the clearance may diminish to 15 or 20 per cent of normal The nature of the renal disturbance

electrolytes in the gastric juice The loss of large amounts of highly acid gastric content induces a severe depletion of tissue and plasma chloride and a smaller deficit of sodium the plasma bicarbonate increases in proportion to the chloride loss and associates with the sodium normally equivalent to chloride In the withdrawal of gastric content containing little or no hydrochloric acid depletion of chloride is less pronounced and the bicarbonate excess is correspondingly smaller indeed the acid base equilibrium may not be disturbed Thus "hypochloremic alkalosis is more likely to develop in the patient with duodenal ulcer and gastric hypersecretion than in the normal person or the patient with gastric ulcer The quantitative differences in volume of secretion and gastric electrolytes between these groups are highly significant (Table 42) Curiously the stomach may continue to secrete large amounts of highly acid gastric juice despite extreme depletion of the serum electrolytes

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finding was the accumulation of calcium in the renal collecting tubules Identical changes have been observed in fatal cases of alkalosis secondary to continuous gastric aspiration in patients who have never taken alkali Furthermore, they can be induced by the experimental depletion of chloride in animals and prevented by the concomitant parenteral administration of sodium chloride The deposition of calcium presumably is related to an alteration in the physicochemical state of the urine with the precipitation of calcium phosphate and calcium carbonate

The prolonged administration of moderate quantities of alkali does not usually alter renal function (urea clearance) However in the presence of alkalosis a previously normal clearance may decrease temporarily We have not observed significant anatomic changes in the kidney following the long continued use of sodium bicarbonate or calcium carbonate in patients succumbing to unrelated causes

Hypercalcemic Syndrome and Mild Alkalosis in a Patient with Chronic Duodenal Ulcer and Hypertension

An unusual syndrome rarely may be encountered in patients with peptic ulcer characterized by a history of prolonged and excessive intake of milk and absorbable alkali hypercalcemia without hypercalcuria or hypophos phatemia normal serum alkaline phosphatase severe renal insufficiency with azotemia mild alkalosis and calcinosis manifested especially by an ocular lesion resembling band keratitis Improvement follows the discon tinuance of soluble alkali and a decrease in the intake of milk Many of these features were observed in the following case

Case 3 A D a man aged fifty four had recurrent duodenal ulcer for twenty five years with intermittent use of alkalies In March 1949 the patient was placed on an hourly schedule of milk and cream and 1 teaspoonful quantities of calcium carbonate Six weeks later the intake of alkali was decreased to six doses daily The blood pressure was 150/100 In August the antacid was discontinued entirely Ten days before admission to the hospital in September the patient had frontal headaches vague muscular aches and anorexia followed subsequently by nausea vertigo and conjunctivitis There was no history of the ingestion of vitamin D The blood pressure now was 170/110 Band keratitis was not observed

Roentgenographic studies disclosed a calcific density in the left hemisphere of the brain just beyond the coronal suture The long bones appeared normal there was no calcification in the renal areas Therapy included 1100 cc of whole blood for a moderate anemia and 1500 cc of 5 per cent dextrose in isotonic saline solution intravenously for the correction of a mild alkalosis In addition to milk and cream a total of 208 gm of calcium carbonate and 24 gm of magnesium carbonate were administered during the first ten days of hospitalization (September 4 to 13 1949) Subsequently the patient was maintained on six bland feedings daily without milk cream or alkali The urine six months earlier had been free of albumin a few hyaline casts were reported on one oc casion the specific gravity was 1 022 to 1 024 Now the urine contained one or two plus quantities of albumin and occasional hyaline and granular casts the specific gravity varied between 1 010 and 1 016 there were no doubly refractile fat bodies The Sulko witch test gave usually a 2 plus reaction for calcium in the urine The plasma proteins totaled 7 24 gm per cent and the albumin globulin ratio was normal The urea clear ance upon admission measured 11 per cent of average normal it rose later to 75 per cent of normal The symptoms and abnormal chemical findings gradually subsided after the discontinuance of milk and cream and alkali

The patient is in good health at the present time eighteen months later The urine is normal except for a slightly lowered specific gravity The results of various chemical analyses are as follows

has not been fully clarified although in some respects it resembles a lower nephron nephrosis In hypochloremic alkalosis the glomerular filtration rate effective plasma flow and the maximal tubular excretory capacity are markedly diminished probably as a consequence of the reduction in extracellular fluid decreased cardiac output and altered circulatory dynamics leading to renal vasoconstriction The kidneys usually recover their original function within several weeks or months after restoration of electrolyte and fluid balance occasionally renal function (urea clearance) may be persistently decreased for six or eight months or even longer

Recurrent Severe Hypochloremic Alkalosis, Terminating Fatally Calcium Precipitate in Renal Collecting Tubules

Histologic examination in fatal cases of hypochloremic alkalosis may demonstrate degenerative and regenerative changes in the tubular epithelium and precipitates of calcium salts in the collecting tubules of the kidney as illustrated by the following unusual case

Case 2 B G a woman aged thirty seven with a history of ulcer distress for five years was hospitalized on five occasions during the subsequent six years twice because of massive hemorrhage Moderate amounts of alkali (sodium bicarbonate calcium carbonate and tricalsate) were taken during this time The blood pressure was moderately elevated Numerous urine analyses were normal the specific gravity ranged from 1 008 to 1 021 The urea clearance initially measured 65 per cent of average normal A gastroduodenostomy was performed for the relief of pyloric stenosis However recurrent vomiting culminated in one bout of mild alkalosis and three episodes of severe alkalosis On one occasion the serum carbon dioxide content rose to 62 mM per liter and the *pH* to 7 65

Physical examination disclosed flexor spasms of both forearms and hands numbness of the face and a positive Chvostek sign The serum calcium was reduced to 6 2 mg per cent The blood urea nitrogen increased and the urea clearance diminished temporarily Prolonged aspiration of the stomach later resulted in another episode of severe alkalosis the serum chloride decreasing to 56 7 mM per liter and the carbon dioxide content rising to 41 mM per liter The patient after recurrent vomiting finally was admitted in a semi comatose state with hyperactive reflexes and fibrillary muscular twitchings The serum chloride measured 71 mM per liter the carbon dioxide content 48 5 mM per liter and the pH 7 7 Clonic convulsions developed despite the immediate intravenous infusion of salt solution and the patient died within several hours

Autopsy disclosed an acute gastric ulcer high grade stenosis of the pylorus and chronic duodenal ulcer with marked stenosis and perforation into the head of the pancreas Two parathyroid glands were identified and appeared normal histologically The kidneys weighed 100 and 112 gm the surfaces were diffusely granular and pale Histologic examination demonstrated an increase in fibrous tissue thickening of the walls of some arterioles and hyalinization and sclerosis of glomeruli The tubules varied considerably in appearance some were widened and lined with cuboidal cells the epithelium contained hyperchromatic nuclei and occasional mitotic figures indicative of active cell proliferation The epithelium in occasional distal collecting tubules was extensively desquamated the lumina were completely obstructed by loose epithelial cells and granular protein debris Many collecting tubules were filled with coarse bluish colored or almost colorless granular masses (hematoxylin eosin stain) which assumed a black color with the von Kossa stain for calcium Foci of interstitial inflammation were present adjacent to the calcium filled tubules The alkaline phosphatase content of the kidneys was markedly diminished (Gomori stain)

Although considerable renal damage was demonstrable in this case much of the parenchyma appeared normal The hyalinization of glomeruli increased fibrous tissue atrophy of tubules and arteriolar thickening are attributable to the chronic hypertension The most interesting histologic

The symptoms usually subside promptly after the reestablishment of normal electrolyte and fluid balance however delay in the treatment of severe alkalosis has resulted in coma and death in spite of belated restoration of the acid base balance to normal levels

DIAGNOSIS

The prompt recognition of alkalosis depends upon an awareness of its possible occurrence during the ingestion of soluble alkali and during the vomiting or aspiration of acid gastric content as well as upon familiarity with the clinical manifestations of the syndrome Accurate diagnosis is established only by measurement of the plasma electrolytes The plasma or serum carbon dioxide content *p*H and chloride should be determined routinely and at frequent intervals during the administration of large quantities of alkali and during gastric aspiration these analyses should be obtained without delay in patients who have been vomiting or who present symptoms suggestive of alkalosis

Measurements of the serum sodium and potassium are desirable to define the acid base disturbance more precisely and thus facilitate efficient replacement therapy these analyses now can be made more frequently with the flame photometer Inasmuch as the plasma chloride level is maintained until the tissue chlorides are considerably depleted and since furthermore the plasma chloride may be increased by hemoconcentration this analysis alone does not always reflect accurately the degree of chloride loss Serial measurements of the chloride content of the urine provide important information in this regard

Recent studies suggest that provided renal and adrenal function are normal water and salt balance is properly maintained if the daily urine volume exceeds 1500 cc and its salt concentration approximates 3 gm per liter estimates of adequate salt excretion vary from 1 to 5 or 10 gm of sodium chloride per twenty four hours

The test described by Fantus[8] can be performed rapidly and easily with the following material a small test tube a small pipette or dropper 20 per cent solution of potassium chromate (the indicator) 2 9 per cent solution of silver nitrate and distilled water The procedure is as follows 10 drops of urine are measured into the test tube the pipette is rinsed and 1 drop of potassium chromate is added the pipette is again rinsed thoroughly and the silver nitrate is added dropwise the test tube being shaken after each drop The end point is a sharp change in color from yellow to brown The number of drops required to reach the end point indicates the concentration of chloride in the urine expressed as grams of sodium chloride per liter e g 5 drops represent 5 gm An output less than 3 gm per twenty four hours probably should be regarded as below normal

Scribner[31] recently has described a relatively simple accurate and inexpensive method for the determination of chloride in the urine plasma and other body fluids An acidified sample is titrated with mercuric nitrate in the presence of diphenylcarbazone The mercuric nitrate reacts with the chloride in the sample to form soluble but un ionized mercuric chloride When all the chloride is used up the excess mercuric ion gives a strong purple color with diphenylcarbazone

DATE	CA (mg %)	P (mg %)	ALK PHOSPHATASE (BOD UNITS)	CL (mM /L)	CO_2 (mM /L)	pH	NA (mM /L)	K (mM /L)	BUN (mg %)	CREATININE
9/4/49	13	—		91 6	33 5	7 54			57	
9/6				92 4	30 0	7 48			60	
9/8				94 8	31 3	7 48				
9/10	13 8	6 5		96 4	29 6	7 49			80	10
9/12			6 9				132 4	5 3	92	
9/16	11 5	5 4		101 0	24 0	7 53	135 0	4 9	82	
9/26	8 9	2 9		104 0	26 2	7 41	137 5	4 8	32	
9/28			7 2							
10/3	8 7	2 3							18	
11/7	11 4	3 9								2
1/20/50									19	
5/13									16	

CLINICAL MANIFESTATIONS

The clinical manifestations of alkalosis generally are related to its effects upon the central nervous system and to the consequences of dehydration Mild alkalosis usually does not produce symptoms subjective complaints may be minimal or absent in moderately severe chemical alkalosis Wide individual variations in symptomatology are encountered

In alkalosis complicating the medical management of peptic ulcer with soluble alkali and gastric aspiration symptoms usually appear between the fourth and tenth days of treatment although in some patients not until after several weeks have elapsed The earliest complaints are a distaste for the milk and cream and alkali and anorexia Nausea vomiting generalized weakness vertigo dull headache and dryness of the mouth develop concurrently or subsequently The respirations may be shallow and slow because of depression of the respiratory center by the increased serum pH An acute chemical conjunctivitis may develop presumably attributable to the increased pH of the lacrimal secretions Changes in personality and temperament such as increased irritability moodiness apathy disorientation and mental confusion are frequent the clinical picture may be that of an acute toxic psychosis Drowsiness may progress to deep coma Muscular twitchings and hyperactive reflexes are not uncommon Weakness and hypotonia of the skeletal muscles may develop probably as a consequence of diminished concentrations of potassium in the serum In contrast to the alkalosis of respiratory origin tetany is rare probably because the concentration of calcium ion and the carbon dioxide tension of the blood usually remain within normal limits

These symptoms in general are characteristic of salt and water depletion and are accompanied by the physical signs of dehydration In rapidly developing severe hypochloremic alkalosis the peripheral vascular collapse with fall in blood pressure feeble pulse cyanosis and coma are identical with the clinical features of acute adrenal insufficiency It is of interest that salt depletion in dogs produces a form of peripheral vascular collapse resembling that observed in traumatic shock the plasma volume cardiac output circulation rate and blood pressure all decline sharply and protein disappears from the plasma

more rapid rates of injection will cause toxic reactions The efficiency with which hypochloremia may be corrected with ammonium chloride is illustrated in the two following cases

Prompt Correction of Severe Chloride Deficit with Ammonium Chloride

Case 4 J E C a man aged forty six had gastric and duodenal ulcers After one week of ulcer therapy including nightly gastric aspirations the patient had symptoms of weakness nausea and mental depression The serum chloride was 80 mM per liter the carbon dioxide 44 C and the pH 7 68 During the next twelve hours 1000 cc of 2 per cent ammonium chloride in isotonic saline solution were administered intravenously and 1000 cc of isotonic saline solution given by hypodermoclysis At the conclusion of therapy the serum chloride was 103 6 mM per liter the carbon dioxide 23 6 mM per liter and the pH 7 44 The symptoms of alkalosis subsided In this case an additional 4 gm of sodium chloride by mouth proved insufficient to prevent the chloride depletion induced by nightly gastric aspiration

Case 5 R L H a man aged fifty two had a duodenal ulcer with hemorrhage Frequent vomiting and the aspiration of large quantities of highly acid gastric content resulted in a severe alkalosis accompanied by an acute toxic psychosis The serum chloride measured 79 8 mM per liter the carbon dioxide content 52 and the pH 7 66 Three hours later after the infusion of 400 cc of 2 per cent ammonium chloride in distilled water the values were chloride 83 4 carbon dioxide 47 6 and pH 7 61 Six hours later after the intravenous administration of 1500 cc of 2 per cent ammonium chloride and 1500 cc of 5 per cent dextrose the chloride was 101 7 mM per liter and the carbon dioxide 9 2 mM per liter The psychotic manifestations subsided promptly

Replacement of the intracellular losses of potassium is necessary in occasional instances of severe "hypochloremic" alkalosis Failure to correct the deficiency of potassium has been suggested as the cause of the ineffectiveness of isotonic sodium chloride solution in refractory alkalosis Potassium chloride can be administered by mouth in daily doses of 3 to 6 gm or intravenously as a 2 per cent solution in distilled water A quantity of 0 26 gm of potassium chloride per kilogram per twenty four hours is considered to be a safe amount when given by vein in not less than four hours or by hypodermoclysis in eight hours

Peters has suggested a solution containing approximately 100 mEq of potassium (7 5 gm of potassium chloride in 500 cc of distilled water) which can be diluted with 500 to 1000 cc of isotonic saline or glucose solution Burnett and Burrows[1] have administered an isotonic potassium solution containing 30 mEq each of potassium and chloride per liter this may be prepared by the mixture of potassium chloride 2 25 gm glucose 50 gm and distilled water enough to make 1000 cc Darrow and Pratt[6] have suggested a mixture containing approximately 6 gm of sodium chloride and 2 7 gm of potassium chloride per liter the solution is injected subcutaneously at a slow rate over a period of four or more hours for intravenous infusion it should be diluted with two or three parts of 5 or 10 per cent dextrose in water

Potassium salts should be administered *only* when direct proof of potassium deficit has been obtained and *only* after an adequate flow of urine has been established by the prior infusion of sodium chloride and glucose Excessive concentrations of potassium in the blood may cause heart block Serial electrocardiograms should be obtained during therapy the changes attributed to potassium deficiency—low T wave depression of the S T segment prolongation of the Q T interval, inversion of the T waves the presence of U waves and extrasystoles—disappear when the deficit is corrected

TREATMENT

Alkalosis is a potentially serious complication and therefore requires prompt attention The ultimate objective is restoration of normal osmotic and fluid relationships in the intracellular and extracellular fluids The principles of treatment are removal of the cause reestablishment of the normal electrolyte pattern and restoration of plasma volume and renal function The quantitative aspects of therapy and the composition of the solutions to be used vary with the severity of the biochemical disturbance the degree of dehydration and the status of renal function in the individual case The best guides to effective treatment are frequent analyses of the serum electrolytes serial determinations of the chloride content of the urine and the clinical response to therapy Frequent estimations of the hematocrit are desirable as an approximate index of the restoration of plasma volume Accurate daily measurements of body weight may be taken as fairly reliable evidence of changes in body water

In alkalosis caused by sodium bicarbonate the acid base balance usually returns to normal within several days after the discontinuance of alkali the addition of 5 to 10 gm of sodium chloride and ammonium chloride to the diet and the sufficient intake of fluid

In alkalosis resulting from chloride depletion the initial objective is the relief of dehydration Water alone will not suffice for this purpose the lost electrolytes also must be replaced It should be noted in this regard that water taken by mouth rapidly assumes an electrolyte pattern similar to that of the gastric content and thus during persistent vomiting or aspiration may accentuate the electrolyte depletion fluids by mouth therefore should be avoided Acid base and fluid balance will be restored in many cases by the intravenous or subcutaneous infusion of 1500 or 3000 cc of an isotonic (0 85 per cent) solution of sodium chloride or 5 per cent dextrose in physiologic saline solution In the presence of marked sodium deficit with a proportionately smaller reduction in volume of body water ("hypotonic dehydration) 250 to 500 cc of hypertonic salt solution (2 or 3 per cent) may be desirable to avoid the administration of the tremendous quantities of fluid which would be required if isotonic saline solution were used The sodium chloride solutions replace the depleted electrolytes restore the volume of extracellular fluid dilute and decrease the excess bicarbonate in the plasma and promote the excretion of increased quantities of bicarbonate in the urine

The importance of adequate renal function in the restoration of electrolyte and fluid balance and in reestablishing normal osmotic relationships cannot be overemphasized The best clinical index as to the quantity of solution required is the volume of urine the twenty four hour output should be not less than 1500 cc and the chloride content approximately 2 to 5 gm per liter Since the loss of chloride ion quantitatively exceeds that of sodium more chloride may be necessary subsequently A 2 per cent solution of ammonium chloride provides chloride without additional sodium the ammonia combines with carbon dioxide to form urea and the chloride ion is retained A 2 per cent solution is prepared by dissolving 20 gm of ammonium chloride in a liter of distilled water or 5 per cent dextrose Five hundred to 1500 cc may be administered intravenously depending upon the severity of the chloride depletion The infusion should be regulated carefully so that 1 liter of solution is given over a period of three hours

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Hypochloremic alkalosis also is characterized by a negative nitrogen balance due to the increased tissue catabolism and to the insufficient intake of food Since the infusion of large quantities of sodium chloride in the presence of a diminished concentration of albumin will produce edema the development of hypoproteinemia should be combated by the adminis tration of plasma or whole blood if anemia is present or by purified salt poor human albumin Protein hydrolysates also are useful but may be less effective for this purpose since they are rapidly metabolized and excreted Five per cent dextrose should be given to prevent unnecessary destruction of protein and consequent ketosis Protein replacement therapy is particu larly indicated during continuous gastric aspiration and in the preoperative preparation of patients with obstructing peptic ulcer

PREVENTION

Alkalosis complicating the medical treatment of peptic ulcer can be prevented by (*a*) the avoidance of soluble alkali (sodium bicarbonate) (*b*) the intake of a sufficient quantity of fluid to ensure an adequate volume of urine and (*c*) in patients in whom 200 cc or more of gastric content are aspirated nightly by the daily oral administration of 5 to 10 gm of sodium chloride or sodium and ammonium chloride in enteric coated tab lets During continuous aspiration of the stomach accurate records should be kept of the quantity of gastric aspirate and the volume of urine The serum electrolytes and the chloride content of the urine should be measured daily and appropriate replacement therapy maintained

Experience indicates that as much as 4500 cc of isotonic salt solution and 5 per cent dextrose may be required daily to sustain the acid base and water balance in patients with duodenal ulcer undergoing twenty four hour gastric aspiration Constant awareness of the possible occurrence of al kalosis and the use of adequate preventive measures will greatly decrease the incidence of this complication Prompt effective treatment based upon an understanding of the pathogenesis of the electrolyte disturbance should minimize or obviate its potentially harmful effects

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INCIDENCE

Acute perforation is a fairly common complication of ulcer which occurs more frequently in the untreated cases It is probably not seen in more than 2 per cent of patients suffering from peptic ulceration The recent increase in gastroduodenal ulceration has been accompanied by a disproportionately greater increase of acute perforations

Early reports on the incidence of acute perforation showed the sex incidence to be about equally divided However during the past fifty years there has been a progressive decreased incidence in females and an increased incidence in males[10] Yudin[25] in 1939 reported 1335 cases of which 1 9 per cent were females In De Bakey s collected statistics there were 14 339 cases of which 7 7 per cent were females There is no satisfactory explanation of this fact Active peptic ulcer is rare in pregnant women and acute perforation practically unknown Sandweiss Saltzstein and Farbman[18] observed only one active peptic ulcer in 70 310 consecutive admissions of pregnant women and reported one perforation

Perforation of an ulcer may occur at any age In a collected series of 6875 cases[7] 73 per cent occurred in the third and fifth decades 4 per cent in the first and second decades and about 23 per cent in patients over fifty years of age Cases have been reported in infants under one year of age In the younger age group most perforations are duodenal Sixty five per cent of perforated duodenal ulcers occurred in patients under forty years of age conversely 60 per cent of perforated gastric ulcers occurred in patients over forty years of age

Acute perforations are much more frequent in duodenal than in gastric ulcers Statistics vary greatly because of the difficulty in determining at the time of operation the exact location of the perforation in relation to the pylorus Yudin[5] however made a careful examination of 928 gastric resections for acute perforated ulcer and found that 87 5 per cent were duodenal

HISTORY

Characteristically the perforation is marked by sudden excruciating pain in the midepigastrium accompanied frequently by collapse The pain subsequently spreads to the entire abdomen although it sometimes remains localized It is important in taking the history to determine where the *initial* pain occurred Further the abdominal pain is so agonizing and abrupt in onset that unless the patient is specifically questioned he will often fail to describe the characteristic shouldertip pain which is frequently present It is most often localized to the right shoulder but may present in the left or in both shoulders This radiation is not diagnostic but suggestive and is due to irritation of the diaphragm by free air or gastroduodenal contents

Nausea and vomiting are generally present but are not severe frequently the vomiting is induced by the patient in the belief that relief will be achieved Medications taken orally are usually promptly returned with intensification of the pain

In about 75 per cent of cases a history of preceding ulcer disease will be elicited Reperforation has been reported in 1 to 5 per cent of perforated ulcers [13] [3] with as many as five episodes of perforation occurring in the

Chapter 63

ACUTE PERFORATION OF ULCER

RALPH COLP AND LEONARD J DRUCKERMAN

Acute perforation of a peptic ulcer is a most serious and lethal complication It occurs when the ulceration penetrates all the layers of stomach or duodenum forming a free communication between the interior of these organs and the free peritoneal cavity When the ulcer ruptures into an adjacent viscus a chronic perforation exists (see Chap 64) When the perforation is small and the leakage minimal the term formes frustes or subacute perforation has been applied When a sudden communication is made between the interior of the stomach or duodenum and the peritoneal cavity permitting a relatively free flow of the gastroduodenal content into the peritoneal cavity the classic picture of acute perforation of an ulcer ensues Peritonitis inevitably follows resulting in a high percentage of deaths in untreated cases and a moderate mortality even in treated cases

The immediate effect on the peritoneum of rupture of an ulcer is the production of a chemical peritonitis caused by the irritative effect of the gastric bile and pancreatic juices If the stomach is empty this early peritonitis is largely chemical becoming definitely a bacterial peritonitis only after a lapse of several hours Early cultures are usually sterile but the percentage of positive cultures increases rapidly after the first six hours some investigators reporting 100 per cent positive cultures after twelve hours The organisms usually found early are streptococci and staphylococci only later is the colon bacillus found If however the patient has just partaken of food or fluid this too will be poured into the peritoneal cavity and the bacterial peritonitis will occur much earlier

It can readily be seen therefore why patients operated upon early have a relatively good prognosis for they are usually in the stage of chemical peritonitis On the other hand patients operated upon late in the course of the disease have a poor outlook for they all have a well established bacterial peritonitis

Innumerable series of cases have been reported emphasizing the rising mortality rate which occurs with the lengthening of the time interval between perforation and operation The largest compilation of such series was made by DeBakey in 1940[7] He reported the mortality rates in 7683 cases as follows

OPERATED UPON	MORTALITY RATE
In 6 hours	10 5%
In 12 hours	21 4%
In 18 hours	38 5
In 24 hours	62 4 %
After 24 hours	61 5 %

The past decade has seen the advent of many therapeutic aids which have served appreciably to lower the appalling mortality figures just cited yet acute perforation continues to remain a most serious complication of chronic peptic ulcer

LABORATORY AIDS

The most valuable aid in diagnosis is afforded by x ray examination of the abdomen This will demonstrate the presence of pneuoperitoneum in more than two thirds of the cases of acute perforation [11] Films are taken

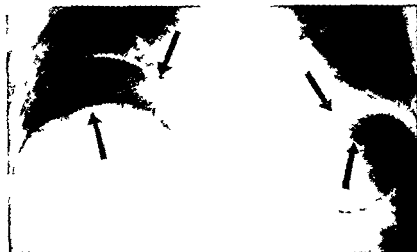


Fig 157 Large pneumoperitoneum demonstrated with the patient in the *erect position* Upper arrows point to diaphragm lower arrows to free air

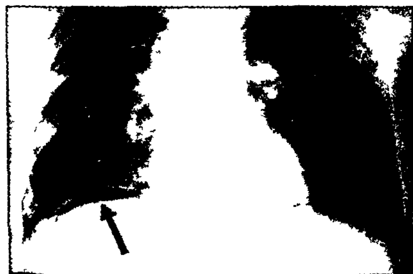


Fig 158 Small pneumoperitoneum

with the patient sitting up or lying on the left side Barilell[2] has empha sized the importance of *keeping the patient in this position* for a few minutes before taking the picture and has suggested that this will result in a greater percentage of positive films Air when present is seen under the diaphragm or just under the lateral abdominal wall Bockus[5] states

same patient Although hemorrhage in association with perforation is rare it may occur

PHYSICAL EXAMINATION

Usually the patient lies quite still on his back with the knees flexed for motion of any sort intensifies the pain Temperature early in the course of the disease is subnormal and is a part of the mild picture of shock which accompanies perforation After several hours the temperature becomes elevated the pulse rapid the tongue dry and the patient appears pinched and anxious

The abdomen is generally rigid and the term "boardlike rigidity" has become classical This extreme degree of rigidity may be confined to the upper abdomen if the spillage of gastroduodenal contents has been minimal If however the patient has recently eaten and a large amount of gastric contents has escaped into the peritoneal cavity this rigidity may rapidly involve the entire abdomen

Tenderness is usually generalized being most marked in the upper abdomen Occasionally when the spillage has mainly gravitated down the right lumbar gutter to the right lower quadrant tenderness may be most marked in this location suggesting a diagnosis of acute appendicitis with which acute perforated ulcer is not infrequently confused In men with well developed abdominal musculature the tenderness may be less marked for the rigid musculature prevents the examining hand from exerting any great pressure on the intraperitoneal structures

Percussion of the right anterior chest and right upper quadrant will often disclose the absence of liver dullness caused by a layer of free intraperitoneal air interposed between the liver and the chest or abdominal wall This absence of liver dullness must be viewed with a degree of caution in the large barrel chested persons in whom it is normally present and in those with marked distention of the colon Abdominal auscultation will usually fail to elicit the sounds of normal peristaltic activity Rectal examination should always be done to aid in the differential diagnosis

"FORMES FRUSTES" TYPE

Not all perforated ulcer cases present the typical picture described There is a type which is extremely difficult to recognize and has been called subacute perforation or "formes frustes" This may be as frequent as the classic perforation but is usually not diagnosed as such because it is mild and atypical In the "formes frustes" variety there is a sudden but trifling escape of gastroduodenal content with early spontaneous closure of the perforation The amount of leakage is minimal producing a localized receding right upper quadrant peritonitis As a rule the patient complains of sudden severe upper abdominal pain which within a few hours is replaced by a dull ache Physical signs are usually only right upper quadrant tenderness and spasticity Roentgenograms may or may not show free air in the peritoneal cavity

These patients frequently recover without a diagnosis being made and without formal treatment Singer and Vaughan [1] emphasize the fact that these cases are often misdiagnosed and overlooked

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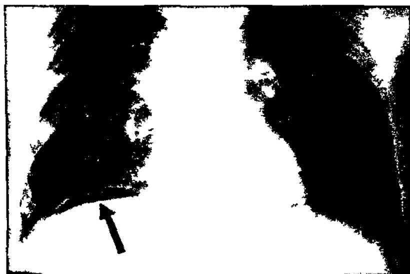


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sides and deep tenderness may be elicited by slow firm pressure in the lateral aspect of the left loin *This is probably due to manual pressure on the tail of the pancreas* Rigidity may be marked but frequently is not boardlike and not generalized Pneumoperitoneum is not present Glycosuria is frequent and a trace of bile may often be found in the urine The serum amylase is usually elevated but too much credence should not be placed upon this finding for evidence has been adduced in both animals and man that in perforated lesions of the upper gastro intestinal tract the amylase can be quickly absorbed from the peritoneum and produce high blood levels [14, 16] Nevertheless the blood amylase may be of great importance for Raffensperger[17] has pointed out that elevations above 500 mg are almost invariably due to acute pancreatitis increases below *that figure may be due to perforated ulcer peritonitis from* other causes intestinal obstruction or uremia Peritoneal puncture will not infrequently obtain the typical dark brownish tan "beef broth" fluid in acute pancreatitis and purulent or bile stained fluid in perforated ulcer

Acute cholecystitis usually presents no difficulties for the onset is with typical biliary colic the temperature is elevated the signs of peritoneal irritation are limited to the right upper quadrant and frequently a mass is palpable If however the gallbladder perforates the ensuing generalized peritonitis can mimic a perforated ulcer The history however will establish the fact that after several hours of severe localized pain there was sudden diffuse pain Peritoneal puncture is of little value for bile may be present in either condition The urine may contain bile

Acute small bowel obstruction may occasionally be confusing especially when there is an associated compromising of the circulation of the bowel by twist or strangulation The finding of a scar on the abdomen will offer a lead The pain is colicky and is associated with intractable vomiting of copious quantities of fluid having the sweetish smell and light brown color of high intestinal contents Rigidity may be present but is rarely boardlike Tenderness is most marked in the lower abdomen Roentgenograms reveal the absence of *pneumoperitoneum* and the *presence* of dilated loops of jejunum Peritoneal puncture should not be done when this condition is suspected it is far too dangerous

Mesenteric thrombosis may simulate a perforation There is frequently *a history of cardiovascular disease The pain is often colicky* and shoulder pain is absent Some distention is present and the rigidity is slight Vomiting and diarrhea are more frequent and may be bloody Peritoneal puncture may produce a reddish fluid

The gastric crisis of central nervous system syphilis can be confusing for the patient may suffer severe abdominal pain and exhibit generalized tenderness and rigidity These patients do not as a rule have a past history of ulcer disease they tend to move about in bed rather than lie quietly and rigidity is rarely as marked Liver dullness is not obliterated the white blood cell count is normal and pneumoperitoneum is not present Peritoneal puncture is unproductive

Other medical conditions may on occasion offer difficulties Acute coronary thrombosis may be associated with severe epigastric pain shoulder pain upper abdominal rigidity and shock A careful history will generally reveal that the shoulder pain radiated down the left arm that vomiting was absent and that dyspnea was not infrequently present Examination will

that in approximately 99 per cent of cases spontaneous pneumoperitoneum demonstrated on x ray films is due to acute perforated ulcer Rarely a rupture in other parts of the intestinal tract may produce this finding

A leukocyte count of 10 000 to 15 000 cells is present at first subsequently it becomes progressively higher Avent Patterson and Chambers[1] found

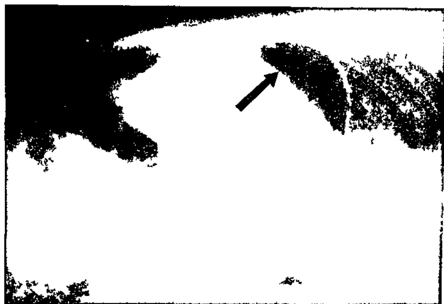


Fig 159 Pneumoperitoneum demonstrated with the patient in the left lateral position Note free air under the right flank and under the diaphragm

that patients with a white blood cell count of less than 6000 had a bad prognosis the mortality rate in this group being 67 per cent

DIFFERENTIAL DIAGNOSIS

The differential diagnosis between ruptured ulcer and conditions which simulate it may present difficulties and in some cases may be impossible being made only after exploratory laparotomy is performed for an obvious peritonitis

Acute appendicitis may easily be confused with perforated ulcer The past history of ulcer pain is often lacking There is no shoulder tip pain and the pain usually *shifts* to the right lower quadrant or the lower abdomen Prostration is minimal Rigidity is usually much less and most marked in the lower abdomen Tenderness is maximal in the right lower quadrant and is less marked in the upper abdomen Rectal examination more frequently reveals tenderness On only the rarest occasion will roentgenograms demonstrate pneumoperitoneum

Acute pancreatitis is most difficult of differentiation and is important to eliminate as a diagnosis for the treatment of acute pancreatitis is now generally recognized as being nonsurgical The location of the pain is in the upper abdomen and in the back about the level of the twelfth thoracic vertebra Vomiting is more frequent Shock is usually more severe Tenderness is usually *most marked in the upper abdomen* equally on both

and a host of Continental surgeons The rationale is simple Since most ulcers which perforate recur and give symptoms why not cure the patient and his disease as well as attend to the perforation when the abdomen is opened? Yudin[24] reported a mortality rate of 7 8 per cent in 231 selected resections for perforated ulcers During the same period the mortality rate was 32 per cent in the group in which simple suture and simple suture and gastro enterostomy were performed Admittedly the poor risk cases were not subjected to resection Bobbio[4] reported 136 recent selected cases with but eight deaths Courty[6] collected 1220 resections performed for acute perforation by twenty three European surgeons with 176 deaths a mortality rate of 14 4 per cent In cases in which the operation was performed during the first six hours (221 cases) the mortality rate was only 7 2 per cent This was compared with 747 cases treated by closure and closure with complementary gastro enterostomy performed by various French surgeons with a mortality rate of 25 per cent in all and a mortality rate of 10 7 per cent in those operated upon in the first six hours There are innumerable reports in this vein [1] [6] with even lower mortality rates reported in smaller series

There seems little doubt from the reported statistics that the immediate mortality of gastric resection performed in *properly selected* cases for perforated ulcer has not greatly increased the mortality that it actually *reduces* mortality as is claimed is to be doubted If a patient is able to tolerate a formidable surgical procedure such as subtotal gastrectomy it is logical to assume that he would survive a simple closure of the ulcer There is an inherent mortality in large surgical procedures and a patient with perforation can be no exception Even if the mortality rate is increased but 2 or 3 per cent by the gastrectomy—and the authors believe it to be greater—gastrectomy has but a small place in the treatment of acute perforated ulcer To our knowledge there is no series in which alternate cases were treated by gastrectomy and simple closure with comparison of the immediate results

Medical Treatment There have been many patients with definitely proved perforated ulcers who refused operation and recovered Almost every surgeon has explored a patient with perforated ulcer to find that the ulcer has already been sealed off by adhesions to the omentum or to a neighboring organ Exploration merely served to uncover the perforation Cultures in the early cases were frequently sterile It would seem that nothing was accomplished by operation which had not already been accomplished by the patient s natural defenses Several surgeons apparently recognized this about the same time

The first to report a series of cases treated medically was Bedford Turner[3] in 1945 He treated six patients with continuous gastric suction rest and parenteral fluids with uneventful recovery in all Taylor treated twenty eight consecutive patients this way twenty four made an uneventful recovery three died from causes not connected with the treatment and one died who might have been saved by immediate operation Subsequently Seeley Hogan Henry and Bertram [9] reported thirty four unselected cases of perforated ulcer treated medically The ages varied from twenty to sixty eight years The interval between eating and perforation varied from ten minutes to twenty four hours The interval between perforation and institution

rarely disclose diffuse boardlike rigidity Peristaltic activity will be heard on abdominal auscultation An electrocardiogram will frequently be of inestimable value Diaphragmatic pleurisy and basal pneumonias occasionally produce abdominal and shoulder pain associated with upper abdominal spasticity and tenderness The cough the localization of pain to the upper abdomen and usually to one side the limited respiratory movement and the physical fluoroscopic and roentgenographic findings of pulmonary pathology will usually elucidate the nature of the disease

TREATMENT

There is at present considerable controversy regarding the treatment of an acute ruptured ulcer The treatment of choice is immediate operation but a small minority have suggested a medical regimen Among the proponents of operation are advocates of simple closure of the ulcer simple closure with gastro enterostomy and finally immediate subtotal gastrectomy

Surgical Treatment Simple closure by suture with or without omental graft is the time honored and by far the most popular method of therapy It has much to recommend it It accomplishes with minimal trauma the immediate goal which is the quick certain closure of a feeding focus which is causing peritonitis It would seem that in the presence of peritonitis and a degree of shock the smallest possible procedure commensurate with stopping the progress of the disease would be best There should be but one end in view—the saving of the patient s life with utter disregard to the tempting possibility of curing the patient of his ulcer disease while the abdomen is open The object should be to cure the perforation not the ulcer Although some years ago this therapy resulted in a rather high mortality recent series suggest that the mortality rate is less than 6 per cent and as low as 1 1 per cent [1, 8, 19] Although it is an established fact that most patients who survive simple suture will be troubled by ulcer again at some future time nevertheless there will undoubtedly be a more propitious time for curative surgery than during the presence of generalized peritonitis

After closure of the ulcer the fluid contents present in the peritoneal cavity especially in the subphrenic and subhepatic spaces the lumbar gutters and pelvis should be thoroughly and systematically evacuated by suction and gentle sponging

Interest in simple closure with simultaneous complementary gastro enterostomy is waning at this time but once had many advocates The trend away from this has more or less followed the trend away from gastro enterostomy in general Originally it was believed that it did not increase the mortality when performed in early cases that it relieved the tension at the site of the sutured perforation that it produced a high percentage of permanent cures and that it was a necessity in the stenotic ulcer or in cases in which closure of the perforation produced a stenosis It has been largely abandoned because most of these beliefs have been found to be untrue It is still used rarely where excessive narrowing of the duodenum has been produced by closure of the perforation

Subtotal resection for ruptured ulcer was first performed by Keetley in 1902 and was subsequently advocated by von Haberer Finsterer Yudin

and a host of Continental surgeons The rationale is simple Since most ulcers which perforate recur and give symptoms why not cure the patient and his disease as well as attend to the perforation when the abdomen is opened? Yudin[24] reported a mortality rate of 7 8 per cent in 231 selected resections for perforated ulcers During the same period the mortality rate was 32 per cent in the group in which simple suture and simple suture and gastro enterostomy were performed Admittedly the poor risk cases were not subjected to resection Bobbio[4] reported 136 recent selected cases with but eight deaths Courty[6] collected 1220 resections performed for acute perforation by twenty three European surgeons with 176 deaths a mortality rate of 14 4 per cent In cases in which the operation was performed during the first six hours (221 cases) the mortality rate was only 7 2 per cent This was compared with 747 cases treated by closure and closure with complementary gastro enterostomy performed by various French surgeons with a mortality rate of 25 per cent in all and a mortality rate of 10 7 per cent in those operated upon in the first six hours There are innumerable reports in this vein [1 6] with even lower mortality rates reported in smaller series

There seems little doubt from the reported statistics that the immediate mortality of gastric resection performed in *properly selected* cases for perforated ulcer *has not greatly increased the mortality* that it actually *reduces* mortality as is claimed is to be doubted If a patient is able to tolerate a formidable surgical procedure such as subtotal gastrectomy it is logical to assume that he would survive a simple closure of the ulcer There is an inherent mortality in large surgical procedures and a patient with perforation can be no exception Even if the mortality rate is increased but 2 or 3 per cent by the gastrectomy—and the authors believe it to be greater—gastrectomy has but a small place in the treatment of acute perforated ulcer To our knowledge there is no series in which alternate cases were treated by gastrectomy and simple closure with comparison of the immediate results

Medical Treatment There have been many patients with definitely proved perforated ulcers who refused operation and recovered Almost every surgeon has explored a patient with perforated ulcer to find that the ulcer has already been sealed off by adhesions to the omentum or to a neighboring organ Exploration merely served to uncover the perforation Cultures in the early cases were frequently sterile It would seem that nothing was accomplished by operation which had not already been accomplished by the patient s natural defenses Several surgeons apparently recognized this about the same time

The first to report a series of cases treated medically was Bedford Turner[3] in 1945 He treated six patients with continuous gastric suction rest and parenteral fluids with uneventful recovery in all Taylor treated twenty eight consecutive patients this way twenty four made an uneventful recovery three died from causes not connected with the treatment and one died who might have been saved by immediate operation Subsequently Seeley Hogan Henry and Bertram[20] reported thirty four unselected cases of perforated ulcer treated *medically The ages varied from twenty to sixty eight* years The interval between eating and perforation varied from ten minutes to twenty four hours The interval between perforation and institution

of therapy was thirty minutes to sixty six hours in eleven patients it was in excess of six hours All recovered Three patients had complications one of which was a subhepatic abscess which required drainage

Seeley s method of treatment featured the use of the Levin tube with constant suction If the patient had recently eaten the stomach was first emptied (*not* lavaged) with a large gastric tube The patient was given morphine as needed and parenteral saline glucose penicillin and sodium sulfadiazine (2 gm intravenously and then 1 gm every four hours) The lower abdomen became soft in twelve hours rigidity disappeared com pletely in thirty six to forty eight hours and peristalsis was elicited on the second or third day On the fifth or sixth day 1 ounce of milk and cream was fed with the Levin tube still in place but clamped off If no abdominal discomfort was manifest the tube was removed and the feedings were increased The sodium sulfadiazine was discontinued on the sixth day and the penicillin on the tenth day Ambulation followed removal of the tube

Seeley stressed the importance of *constantly watching and checking* the Levin tube to make sure that suction is being maintained and stated that if there are insufficient personnel to *insure* constant decompression this treatment was not to be recommended He felt that the properly function ing Levin tube constituted the most important single element in the treatment

Seeley stated that the nonoperative treatment of ruptured peptic ulcers can be used in a majority of the cases with a resulting lowered mortality a decrease in time lost from work a lowered incidence of complications and an easier convalescence for the patient Olson and Norgore[15] how ever have abandoned conservative treatment of perforated ulcer and state that it is now used only in patients who refuse emergency operation

It is difficult in this maze of conflicting statements and statistics to have a clear idea of the proper treatment of a perforated ulcer In the opinion of the authors this simple plan should be followed Patients admitted dur ing the first twenty four hours of their disease should be promptly operated upon and treated by simple suture In the rare case in which the duodenum seems to be definitely stenosed by the closure a complementary gastro enterostomy should be performed After twenty four hours most patients should be treated medically by the methods described Subtotal gastrectomy should be reserved for the rare perforated carcinoma or huge gastric ulcer

Preoperative Preparation Urgent though operation may be it should always be preceded by proper preoperative preparation Shock when present should be treated even though this may necessitate delay in per forming operation Intravenous saline and glucose should be given on ad mission and continued through the postoperative period Blood transfusion may be necessary in some patients Morphine should be withheld until after a diagnosis has been made and then it should be given If possible a Levin tube should be passed and the stomach emptied after which con tinuous suction should be applied If the patient gags and strains it is better to wait till after the perforation has been closed for the straining will not only force more gastric contents into the peritoneal cavity but will further disseminate what has already spilled Frequently if the nose and pharynx have been adequately anesthetized with a surface anesthesia the tube can be passed with practically no discomfort or straining

Anesthesia Despite the oft repeated observation that "it is not the anes

thetic but the anesthetist that is important" there is a general feeling backed by statistical observation that spinal anesthesia is the agent of choice In the occasional elderly patient in the presence of hypertension or cardiac disease general anesthesia should be used (see also Chap 42)

Drainage It would seem that drainage of the peritoneal cavity is rarely if ever indicated in the present surgical treatment of ruptured peptic ulcer Drainage of the abdominal wall may occasionally be done when the tissues have been bathed in the infected peritoneal fluid of a perforated ulcer operated upon late in the course of the disease When the bacterial content of the peritoneal fluid is high it is questionable whether here also with proper irrigation of the wound before suture and adequate antibiotics post operatively primary union cannot frequently be obtained without drainage

Postoperative Care Antibiotics and chemotherapeutic agents which are usually started preoperatively are continued through the first several days after operation It is suggested that 900 000 units of penicillin be given daily and that 0 5 gm of streptomycin be given every six hours to all patients Sodium sulfadiazine may be administered intravenously in doses of 1 gm every four hours Intravenous aureomycin in doses of 200 mg every six hours may be utilized in the desperately ill patient where its tendency to produce phlebitis is of slight importance when weighed against its powerful antibiotic action

Constant suction with the Levin tube is maintained until the paralytic ileus that accompanies peritonitis disappears This usually is on the third or fourth day at which time small fluid feedings are started and the patient is ambulated

About 3000 cc of intravenous fluids are supplied daily until oral feedings are begun About 5 gm of sodium chloride should be given daily in this fluid unless the drainage from the Levin tube is unusually large indicating large chloride loss which should be restored Parenteral vitamins are advised

Postoperative Complications The innumerable complications which may follow any major surgical procedure are of course seen after operation performed for perforated ulcer and need not be discussed here The complications which are inherent in the condition are mainly infections of the peritoneum and the wound

Peritonitis especially in late cases can be progressive and fatal Localized areas of infection within the peritoneal cavity occur commonly in three locations the subphrenic spaces the subhepatic spaces and the pelvis Unexplained fever after the first week is most likely due to walled off infection in these areas provided the chest is normal and the wound is clean Right subphrenic abscesses occur more frequently than left are often accompanied by a sympathetic pleural effusion and almost always require surgical drainage The majority of subhepatic and pelvic abscesses may be expected to resolve Wound infections are frequent and wound dehiscence and evisceration not uncommon Rarely a sutured ulcer will reperforate bleed or obstruct in the immediate postoperative period

PROGNOSIS

The immediate mortality has been discussed In the light of recent reported series and because of the advances in the use of antibiotics the

authors feel that the mortality when proper treatment is administered should be less than 5 per cent It is to be remembered however that this will vary with the interval between perforation and treatment the nature volume and bacterial flora of the stomach contents at the time of perforation the size and location of the perforation the potency of the natural defenses and the age of the patient In general perforated gastric ulcers have a higher mortality rate than duodenal ulcers

The ultimate prognosis is not good The old belief that "perforation cures an ulcer has long since been proved incorrect This belief probably arose from the fact that after a perforation there is often a remission of symptoms for several months This is not due to the perforation but rather to the bed rest diet convalescent care and perhaps the altered mental outlook of the patient Sooner or later however the ulcer usually returns for recurrence in the ulcer diathesis is the rule rather than the exception Illingworth Scott and Jamieson[9] were able to do five year follow up studies on 596 patients who had recovered from perforated ulcer In *each postoperative year* roughly 2 per cent suffered reperforation 1 per cent suffered a hemorrhage and 2 per cent found it necessary to be reoperated upon for relief of symptoms Within five years 30 per cent were well but 70 per cent had had a mild or severe recurrence of disease Illingworth stresses the fact however that most of these patients were not given the benefit of medical treatment and it is to be expected that these figures would be considerably lowered with such treatment (see Chap 47) In general however more than 50 per cent of all patients who have had a perforation may be expected to suffer further manifestations of ulcer disease within five years

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Chapter 64

PERFORATED WALLED OFF GASTRODUODENAL ULCER

JULIAN M RUFFIN

DEFINITION

Before beginning a discussion of this subject it is important that one have clearly in mind what is meant by a perforated walled off gastroduodenal ulcer" The term "perforated ulcer usually refers to an ulcer which has ruptured into the free peritoneal cavity with the development of generalized peritonitis With few exceptions this occurs only in ulcers located on the anterior wall of either stomach or duodenum The diagnosis and treatment of this complication of ulcer are discussed in the preceding chapter

On the other hand ulcers located on the posterior wall of either the stomach or duodenum rarely perforate into the free peritoneal cavity As the ulcer deepens it may erode through the entire thickness of the wall of the stomach or duodenum and invade the underlying structures In the early stages of perforation this produces an inflammation in the invaded organ sometimes with a surrounding inflammatory mass The base of the ulcer is actually formed by the underlying organ (Figs 160 and 161) In general this pathologic process takes place without abscess formation If

healing of the ulcer occurs the inflammation subsides leaving adhesions of varying degrees of density and the site of the ulcer becomes firmly adherent to the underlying structure An ulcer which perforates the wall of

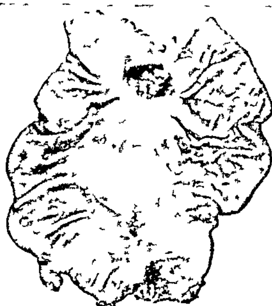


Fig 160 Large gastric ulcer which has perforated into the pancreas

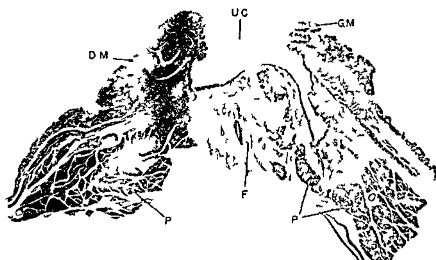


Fig 161 Tissue section showing a prepyloric ulcer which has perforated into the pancreas *U C* ulcer crater *P* pancreas *F* fibrous tissue *G M* gastric mucosa *D M* duodenal mucosa (Photograph by Carl Bishop)

the stomach or duodenum and involves the underlying structures in the manner described is known as a "perforated walled off ulcer" Some authors prefer the terms "penetrating ulcer" or "chronic perforation" to "perforated walled off ulcer"[1] However the terms are frequently used interchangeably

STRUCTURES INVOLVED

The organ most frequently involved by this complication of ulcer is the *pancreas* In a series of 100 consecutive cases of perforated walled off gastroduodenal ulcer confirmed by operation the ulcer perforated into the pancreas in seventy six patients (Table 43 also Fig 163) The liver was in

Table 43 100 Consecutive Cases of Perforated Walled off Gastroduodenal Ulcer Confirmed by Operation

(Duke Hospital)

STRUCTURE INVOLVED	DUODENAL ULCER	GASTRIC ULCER	TOTAL
Pancreas	70	6	6
Liver	6	3	9
Inflammatory mass adjacent to ulcer	8	0	8
Biliary tract	5†	1	6
Transverse mesocolon	0	1	1
Total	0	30	100

Localized abscess present in one case

† In ... gallbladder without actual perforation into biliary tract A sinus tract was present in one (Fig 164)

volved in nine patients and a large inflammatory mass adjacent to the ulcer was found in eight Involvement of the gallbladder without actual perforation into the biliary tract occurred in six cases and in one patient the ulcer *perforated into the transverse mesocolon*

There are isolated reports of ulcers which eroded into the gallbladder or common bile duct into the pleural space into the heart into the aorta or *into the spleen* [7, 1] *Gastroduodenal fistula from an ulcer has also been* reported [13] Perforation of a gastroduodenal ulcer into the colon is rare [8] but it is fairly common for a jejunal or stomal ulcer to rupture into the colon with the formation of a gastro jejunocolic fistula (see Chap 57) Not infrequently a stomal ulcer will perforate and become sealed off by the anterior abdominal wall [9]

INCIDENCE

The incidence of perforated walled off gastroduodenal ulcer is unknown The reasons for this are readily apparent First relatively few of these patients come to autopsy Out of 5000 autopsies at Duke Hospital in the last twenty years there were only three in which evidence of a perforated walled off gastroduodenal ulcer was found The infrequency of this finding at autopsy is confirmed by other authors [10] Second the diagnosis of this condition by roentgenogram is usually difficult and frequently impossible [14] The only other reliable source of information concerning the incidence of this complication is exploratory laporotomy The surgeon can demonstrate easily the *perforation of a gastric ulcer into underlying structures However* it is sometimes difficult to determine if a posterior wall duodenal ulcer has actually invaded the pancreas This is especially true of the postbulbar ulcer

Since only 10 to 15 per cent of ulcer patients come to operation it is apparent that data derived from this source concerning the incidence of

perforated walled off ulcer would not give a true picture of the actual number of patients who have this complication However it is generally believed and in all probability true that most patients whose ulcer becomes refractory to the usual medical care have a perforated walled off ulcer A conservative estimate would be that 5 per cent of all ulcer patients at one time or another have this complication

CLINICAL PICTURE

History The clinical picture of perforated walled off ulcer is obviously the result of symptoms arising from the ulcer itself and those arising from involvement of adjacent structures The most characteristic feature of the perforated walled off ulcer is a change in the usual ulcer pattern Occasionally the patient can recall the exact time at which this change took place but often the process is slow and the patient merely notices a gradual departure from the usual ulcer picture In general this complication occurs after many years of ulcer symptoms but may develop early in the course of the disease The pain becomes more sharply localized in the epigastrium and much more severe frequently requiring opiates for relief It usually is deep and boring and may be present constantly Occasionally there are attacks of sharp knifelike pain Night pain is a common complaint Food or antacids afford little or no relief and in some patients the pain is actually aggravated by eating Often partial relief is obtained by bending forward in a characteristic posture described by Rivers [11]

The radiation of the pain depends upon the structure involved Since the pancreas is the organ most frequently involved the pain usually radiates straight through to the midback at the level of the first or second lumbar vertebra but occasionally encircles the abdomen [12] In some patients it is located only in the back Rarely it originates in the back and radiates anteriorly over the distribution of the spinal nerves If the liver is invaded there may be no radiation of pain or occasionally it is referred to the right shoulder Rarely an ulcer perforates into the gallbladder or common bile duct [5, 14] usually without producing biliary colic However jaundice has been reported in patients whose ulcer has perforated in the vicinity of the common duct [4] In exceptional cases the pain radiates upward over the anterior chest wall or downward over the lower abdomen Thus an unusual location or radiation of ulcer pain should always make one suspect that a perforated walled off ulcer has developed

Hemorrhage frequently occurs in patients with perforated walled off ulcer In some cases the hemorrhage may be so severe as to overshadow other symptoms Many patients operated upon for repeated hemorrhage have an ulcer which has perforated into the pancreas However massive hemorrhage can occur in the absence of perforation into the underlying organ Likewise many patients operated upon for pyloric obstruction from chronic duodenal ulcer are found to have an ulcer which has penetrated into the pancreas On the other hand pyloric obstruction alone may alter the usual ulcer pattern completely and produce a clinical picture similar to that seen in the perforated walled off ulcer

Constitutional symptoms are minimal Since abscess formation is rare chills or fever is seldom seen Whereas the patient with an uncomplicated ulcer usually wishes to avoid operation these patients are desperate and

frequently demand that something be done These are the truly intractable cases

The histories of 100 consecutive cases of perforated walled off gastro duodenal ulcer confirmed by operation were studied at Duke Hospital Seventy one patients had one or more of the features in the history which have been attributed to perforated walled off ulcer namely change in usual ulcer pattern or character of the pain increased severity of the pain or radiation of the pain to the back In the remaining twenty nine these factors were not mentioned or were not present



Fig 162 Roentgenogram showing large gastric ulcer which at operation was found to have perforated into the transverse mesocolon Note that the neck of the crater is narrower than the base

Physical Findings Since most of these ulcers are located on the posterior wall of either the stomach or duodenum physical findings are minimal or absent Occasionally there is point tenderness in the epigastrium Rarely a palpable tender mass may be demonstrated In general there is no rebound tenderness and no evidence of peritoneal irritation In the exceptional case in which the ulcer has perforated into the region of the common duct jaundice may be present[4] As a general rule the diagnosis of perforated walled off ulcer cannot be made by physical examination

Laboratory Findings Laboratory findings rarely assist in the diagnosis Usually there is no leukocytosis unless an abscess has developed If the pancreas is involved serum amylase may be elevated but many patients with penetration into the pancreas do not show this finding Gastric acidity does not vary materially from that seen in the uncomplicated ulcer nor is occult blood in the stool a common finding

X Ray Findings (see Chapters 20 and 21) Unfortunately the roentgenogram is not particularly helpful in diagnosing this condition especially in duodenal ulcer A deep crater in a gastric ulcer would lead one to suspect that a walled off perforation is present particularly if there is a pouch with a narrow neck or a fluid level within the pouch (Fig 162) However a deep crater in itself does not predicate perforation[14] If the roentgenologist can show that the ulcer is firmly adherent to the underlying structures it is likely that perforation has taken place Pockets of air outside the stomach or duodenum can occasionally be demonstrated and are thought to indicate perforation[6] Great caution must be exercised however not to confuse this with gas in a loop of bowel Demonstration of barium entering the gall

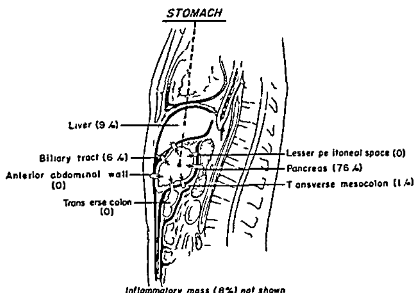


Fig 163 Sagittal section showing more common sites o perforation of gastroduodenal ulcers into surrounding structures Percentages refer to a series of 100 consecutive cases of perforated walled off ulcer confirmed by operation (Table 43) In 8 additional cases the ulcer was walled off by an inflammatory mass

bladder or biliary tree or the formation of a sinus tract is incontestable evidence of perforation (Fig 164) However these are exceptions rather than the rule and in our experience a definite diagnosis of perforated walled off ulcer can be made by roentgenogram in relatively few cases Some roentgenologists however feel that with careful compression technic a tentative diagnosis of walled off perforation can be made in many patients

Gastroscopic Findings The gastroscopic findings in patients with gastric ulcer are described in Chapter 22 Theoretically one might be able to recognize penetration into an underlying structure by gastroscopy but since the base of the ulcer is covered by necrotic material it is usually difficult if not impossible to identify the underlying organ

DIAGNOSIS

With few exceptions the diagnosis of perforated walled off gastroduodenal ulcer can be made with certainty only by operation or autopsy

However correlation of the history with the operative findings in 100 proved cases would lead one to believe that the perforated walled-off ulcer produces a clinical picture which would justify the suspicion if not the diagnosis of this condition The change in the character of the pain the in creased severity the radiation to the back or failure to be relieved by food or antacids would lead one to suspect that a perforated walled-off ulcer has developed Neither the physical findings nor x ray examination was particularly helpful in our series of patients It is probable that most pa tients whose ulcer is refractory to medical treatment have this complication (See also Chap 19)

DIFFERENTIAL DIAGNOSIS

Peptic Ulcer The simple uncomplicated ulcer presents a typical picture which is readily recognized and quite different from that of the perforated walled-off ulcer (see Chap 19)

Pancreatic Disease It is probable that recurrent pancreatitis is the dis ease most commonly confused with perforated walled-off ulcer The char acter the location and the radiation of the pain are frequently identical in both Serum amylase may be elevated in both However concentrations of serum amylase of 500 mg (Somogyi) or above almost invariably indicate acute primary pancreatitis Demonstration by roentgenogram of calcifica tion in the pancreas confirms the diagnosis of chronic pancreatitis Also diminution of pancreatic enzymes determined by analysis of duodenal contents points to the diagnosis of pancreatitis Carcinoma of the pancreas may offer a real problem in differential diagnosis The history of the two conditions may be quite similar and there are a number of patients whose ulcer cannot be demonstrated by roentgenogram In these cases the diag nosis can be made only at operation or autopsy The history of severe upper abdominal pain radiating through to the back and associated with loss of appetite and weight in an elderly person should make one consider strongly the diagnosis of carcinoma of the body of the pancreas

Biliary Tract Disease The pain arising from a cystic or common duct stone is sometimes confused with that of perforated walled-off ulcer How ever the colicky character of the pain the radiation to the right scapula and the presence of jaundice usually differentiate the two conditions It should be noted however that a duodenal ulcer occasionally may perforate into the biliary tree or cause an inflammatory obstruction of the common duct resulting in jaundice[4] (see Chap 26)

Carcinoma of the Stomach The differential diagnosis of carcinoma of the stomach is discussed in Chapter 25 It should be pointed out that the history of perforated walled-off ulcer is sometimes identical with that of carcinoma of the stomach

Diseases of the Spine Some patients with perforated walled-off ulcer have pain in the back only and for this reason are referred to the or thopedist A careful history however usually reveals a relationship between the pain and intake of food Any pain in the midback which cannot be satisfactorily explained on the basis of disease of the spine should make one consider the diagnosis of perforated walled-off ulcer

Miscellaneous The differential diagnosis of other conditions simulating ulcer is discussed in Chapter 26

TREATMENT

Medical These patients should all be hospitalized and treated with a strict dietary regimen (hourly feedings) with antacids and antispasmodics and so forth as described in detail under medical management (Section IV) Opiates are frequently required Constant gastric aspiration at night has been found helpful in the management of many of these patients Usually although the response is delayed it is immediately satisfactory but recurrences are frequent Not infrequently these patients are refractory even to the most rigid hospital medical regimen These patients however should be repeatedly questioned and examined for other complicating factors such as retention food sensitivity psychosomatic disturbances and so on (see Chap 26) Once a diagnosis of walled off perforation" is established and the patient fails to respond satisfactorily to adequate hospital ulcer management one is justified in recommending operation after a preliminary stomach rest period

Surgical The preoperative and postoperative care and the types of operation performed are discussed in Section V

If constitutional symptoms suggest abscess chemotherapy and antibiotics obviously are indicated and surgical drainage may be necessary prior to resection Because of the hazard involved and technical difficulty of removing a perforated walled off duodenal ulcer it is sometimes wiser to do a subtotal gastric resection with exclusion of the ulcer Although adjacent organs may be invaded by the ulcer recovery without sequelae is the rule after resection

CASE REPORTS

Case 1 C Y a forty four year old white man gave a typical ulcer history of ten years duration One year before admission he had had a massive hemorrhage Several weeks later the pain became much more severe radiated through to the back and was no longer relieved by food or antacids as in the past One week prior to admission the pain was present constantly and became so severe as to be incapacitating

Physical examination showed nothing of significance except for slight epigastric tenderness

The laboratory findings were within normal limits free hydrochloric acid 28 clinical units after histamine The stool was negative for blood A gastro intestinal series showed a deformity of the duodenal bulb with a crater

Intensive medical treatment in the hospital afforded little or no relief and he was explored after sixteen days of treatment A duodenal ulcer which had perforated into the pancreas was found at operation A subtotal gastric resection was performed after which he made an uneventful recovery

This patient illustrates the characteristic change from the usual ulcer picture which one frequently sees in patients who have a perforated walled off ulcer

Case 2 J M A a thirty seven year old Negro woman was first seen in the Orthopedic Clinic because of pain in the lower thoracic and upper lumbar spine for the past two years Three weeks previously she had experienced a sudden exacerbation of back pain with girdle type of radiation Accompanying this episode were anorexia nausea and vomiting The initial impression was tuberculosis of the spine or a neurologic disorder with root pain Complete studies of the spine and neurologic examination were negative and she was referred to the Medical Clinic

Physical examination showed nothing of significance

The laboratory findings were likewise within normal limits A gastro-intestinal series showed pyloric obstruction with marked dilatation of the stomach

At operation the patient was found to have a duodenal ulcer which had perforated into the head of the pancreas A subtotal resection was performed followed by clinical recovery

This case is unusual in that the pain was experienced only in the back and was thought originally to be an orthopedic problem

Case 3 M F a 5?-year old white woman gave a typical ulcer history of eighteen months duration *She responded promptly to medical treatment until six months before*



Fig 164 Roentgenogram showing the de elopment of a sinus tract from a perforated walled off d odenal ulcer *A* Ulcer crater in the d odenum *B* Roentgenogram taken 8 week later showing the development of a sinus tract Arrows indicate sinus tract. *C* Another ew of sinus tract (enlarged) *C* Ulcer crater *S* sinus tract *P* pylorus *D* duodenal loop

adm ss on at which time her pain became much more se ere and was no longer relie ed by food or antacids At no time did the pain radiate through to the back

The physical e amination and laboratory findings showed nothing of significance A gastro- nt stinal series re ealed a high ulcer crater on the posterior wall of the stomach A large irregular ulcer which did not ha e the usual appearance of a ben gn lesion was s en by gastroscopy

B ca s of the possibility of carcinoma she was explored and was found to have a large ulc r n the posterior wall of the stomach This had perforated into the body of the

TREATMENT

Medical These patients should all be hospitalized and treated with a strict dietary regimen (hourly feedings) with antacids and antispasmodics and so forth as described in detail under medical management (Section IV) Opiates are frequently required Constant gastric aspiration at night has been found helpful in the management of many of these patients Usually although the response is delayed it is immediately satisfactory but recurrences are frequent Not infrequently, these patients are refractory even to the most rigid hospital medical regimen These patients however should be repeatedly questioned and examined for other complicating factors such as retention food sensitivity psychosomatic disturbances and so on (see Chap 26) Once a diagnosis of walled off perforation" is established and the patient fails to respond satisfactorily to adequate hospital ulcer management one is justified in recommending operation after a preliminary stomach rest period

Surgical The preoperative and postoperative care and the types of operation performed are discussed in Section V

If constitutional symptoms suggest abscess chemotherapy and antibiotics obviously are indicated and surgical drainage may be necessary prior to resection Because of the hazard involved and technical difficulty of removing a perforated walled off duodenal ulcer it is sometimes wiser to do a subtotal gastric resection with exclusion of the ulcer Although adjacent organs may be invaded by the ulcer recovery without sequelae is the rule after resection

CASE REPORTS

Case 1 C Y a forty four year old white man gave a typical ulcer history of ten years duration One year before admission he had had a massive hemorrhage Several weeks later the pain became much more severe radiated through to the back and was no longer relieved by food or antacids as in the past One week prior to admission the pain was present constantly and became so severe as to be incapacitating

Physical examination showed nothing of significance except for slight epigastric tenderness

The laboratory findings were within normal limits free hydrochloric acid 28 clinical units after histamine The stool was negative for blood A gastro intestinal series showed a deformity of the duodenal bulb with a crater

Intensive medical treatment in the hospital afforded little or no relief and he was explored after sixteen days of treatment A duodenal ulcer which had perforated into the pancreas was found at operation A subtotal gastric resection was performed after which he made an uneventful recovery

This patient illustrates the characteristic change from the usual ulcer picture which one frequently sees in patients who have a perforated walled off ulcer

Case 2 J M A a thirty seven year old Negro woman was first seen in the Orthopedic Clinic because of pain in the lower thoracic and upper lumbar spine for the past two years Three weeks previously she had experienced a sudden exacerbation of back pain with girdle type of radiation Accompanying this episode were anorexia nausea and vomiting The initial impression was tuberculosis of the spine or a neurologic disorder with root pain. Complete studies of the spine and neurologic examination were negative and she was referred to the Medical Clinic

Physical examination showed nothing of significance

The laboratory findings were likewise within normal limits A gastro-intestinal series showed pyloric obstruction with marked dilatation of the stomach

11 Rivers A B Syndrome of Peptic Ulcer Perforating into the Pancreas Preliminary Report Proc Staff Meet Mayo Clin 22 290 1947
12 —— and Boodenburg A I Back Pain in Disease of the Gastrointestinal and Accessory Gastrointestinal Tract J.A M A 125 421 1944
13 *Steigmann F and Bach, A. C Peptic Ulcer and Gastroduodenal Fistulae Am. J* Surg 52 355 1941
14 Templeton F E X ray Examination of the Stomach Chicago University of Chicago Press 1944
15 Tylecote F E A Note on Perforation of Gastric Ulcers into the Heart Itself Lancet 2 1613 1913

pancreas A subtotal resection was performed Numerous sections through the wall of the ulcer showed no evidence of carcinoma The patient made a clinical recovery

This case illustrates the fact that a patient may have an ulcer which has perforated into the pancreas without radiation of pain to the back She did have the change in the character and severity of the pain which usually occurs in this complication

Case 4 E P a forty nine year old Negro woman gave a typical history of ulcer pain of eighteen months duration Eight weeks before admission the pain suddenly became severe and radiated to the back She had chills and fever for two days The pain was present constantly and persisted until admission

There was epigastric tenderness but otherwise the physical examination was negative Laboratory findings showed nothing of significance A gastro-intestinal series revealed a large ulcer crater in the duodenum (Fig 164 *A* Under conservative management she improved but the pain recurred from time to time A gastro-intestinal series eight weeks later showed a sinus tract extending from the duodenum toward the diaphragm (Fig 164 *B C*)

At operation an inflammatory mass was found in the region of the hepatoduodenal ligament A partial gastric resection with exclusion of the ulcer was performed and the patient made an uneventful recovery

It is of interest to note that the sinus tract was not visualized at the first x ray examination despite the fact that the ulcer had probably perforated before that time

SUMMARY

It is probable that many of the patients whose ulcer pain is not relieved by intensive medical treatment in a hospital have a perforated walled off gastroduodenal ulcer This complication should be suspected when there is a change in the usual ulcer pattern an increase in severity of symptoms or radiation of pain to the back These patients not infrequently are refractory to medical treatment and if they respond they experience frequent relapses Many of these patients eventually require operation

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